Journal of Human Evolution 152 (2021) 102949

Contents lists available at ScienceDirect

Journal of Human Evolution

journal homepage: www.elsevier.com/locate/jhevol

The *Pan* social brain: An evolutionary history of neurochemical receptor genes and their potential impact on sociocognitive differences

Nicky Staes [a, b, *], Elaine E. Guevara [c], Philippe Helsen [b], Marcel Eens [a], Jeroen M.G. Stevens [a]

[a] Behavioral Ecology and Ecophysiology Group, Department of Biology, University of Antwerp, Universiteitsplein 1, 2610, Wilrijk, Belgium
[b] Centre for Research and Conservation, Royal Zoological Society of Antwerp, Koningin Astridplein 26, 2018, Antwerp, Belgium
[c] Evolutionary Anthropology, Duke University, 130 Science Dr, Durham, NC, 27708, USA

ARTICLE INFO

Article history:
Received 3 June 2020
Accepted 7 January 2021
Available online 10 February 2021

Keywords:
Vasopressin
Oxytocin
Serotonin
Dopamine
Bonobo
Chimpanzee

ABSTRACT

Humans have unique cognitive capacities that, compared with apes, are not only simply expressed as a higher level of general intelligence, but also as a quantitative difference in sociocognitive skills. Humans' closest living relatives, bonobos (*Pan paniscus*), and chimpanzees (*Pan troglodytes*), show key between-species differences in social cognition despite their close phylogenetic relatedness, with bonobos arguably showing greater similarities to humans. To better understand the evolution of these traits, we investigate the neurochemical mechanisms underlying sociocognitive skills by focusing on variation in genes encoding proteins with well-documented roles in mammalian social cognition: the receptors for vasopressin (*AVPR1A*), oxytocin (*OXTR*), serotonin (*HTR1A*), and dopamine (*DRD2*). Although these genes have been well studied in humans, little is known about variation in these genes that may underlie differences in social behavior and cognition in apes. We comparatively analyzed sequence data for 33 bonobos and 57 chimpanzees, together with orthologous sequence data for other apes. In all four genes, we describe genetic variants that alter the amino acid sequence of the respective receptors, raising the possibility that ligand binding or signal transduction may be impacted. Overall, bonobos show 57% more fixed substitutions than chimpanzees compared with the ancestral *Pan* lineage. Chimpanzees, show 31% more polymorphic coding variation, in line with their larger historical effective population size estimates and current wider distribution. An extensive literature review comparing allelic changes in *Pan* with known human behavioral variants revealed evidence of homologous evolution in bonobos and humans (*OXTR* rs4686301(T) and rs237897(A)), while humans and chimpanzees shared *OXTR* rs2228485(A), *DRD2* rs6277(A), and *DRD2* rs11214613(A) to the exclusion of bonobos. Our results offer the first in-depth comparison of neurochemical receptor gene variation in *Pan* and put forward new variants for future behavior−genotype association studies in apes, which can increase our understanding of the evolution of social cognition in modern humans.

1. Introduction

The family of Hominidae includes humans and all species of great apes: chimpanzees, bonobos, gorillas, and orangutans, with chimpanzees and bonobos being humans' closest extant relatives (Prado-Martinez et al., 2014; Besenbacher et al., 2019). Despite these close phylogenetic relationships, humans show unique cognitive skills compared with great apes (Tomasello and Herrmann, 2010). While the extent of these differences, and methods to compare cognition between apes and humans remains a topic of debate (Boesch, 2007; De Waal et al., 2008; Leavens et al., 2019), one of the leading hypotheses is that this difference in cognition between humans and great apes is not simply reflected in a greater degree of general intelligence but also in a quantitative difference in sociocognitive ability (Tomasello and Herrmann, 2010). Sociocognitive ability refers to how individuals understand and respond to social responses and approaches of others (Skuse

* Corresponding author.
E-mail address: nicky.staes@uantwerpen.be (N. Staes).

https://doi.org/10.1016/j.jhevol.2021.102949

and Gallagher, 2011). Its complexity is reliant on the presence of sociocognitive skills like social memory, sensitivity to social cues, empathy, theory of mind and the development and maintenance of affiliative interactions. Studies suggest that apes do not lack these abilities but might differ in degree of sophistication in these skills from humans (Herrmann et al., 2007; Tomasello and Herrmann, 2010; but see; Leavens et al., 2019). Great apes live in complex social groups with individuals that they recognize individually, and with whom they form diversified social relationships, for example, in terms of dominance and friendship (Boesch and Boesch-Acherman, 2000; Stevens et al., 2015). They can also recognize third-party relationships and have some understanding of the behavioral intentionality of social partners (for review, see Call and Tomasello, 2008; Tomasello and Herrmann, 2010). However, it has been argued that humans in contrast to other apes, have evolved sociocognitive skills that allow for higher tolerance and remarkable levels of cooperation (Tomasello et al., 2005; Tomasello and Herrmann, 2010; Apicella and Silk, 2019).

This study aims to contribute to our understanding of the proximate origins of human sociocognitive ability by studying genetic differences as a mechanism underlying differences in sociocognitive skills in apes. To do so, we focus on bonobos (*Pan paniscus*) and chimpanzees (*Pan troglodytes*). These two species diverged from the human lineage most recently of all extant hominoid species (Prado-Martinez et al., 2014; Besenbacher et al., 2019), making them key species for investigating our own evolutionary past and identifying unique human traits (Moore, 1996; MacLean, 2016; Staes et al., 2018; Castellano and Munch, 2020). By comparing traits in *Pan* with those in humans, we can gain an understanding of the genotypic and phenotypic construct of their last common ancestor (the *Pan-Homo* LCA). Bonobos and chimpanzees show marked differences in sociocognitive skills and underlying neural structures that are likely the result of different selection pressures in both lineages (Hopkins et al., 2009; Hare et al., 2012; Rilling et al., 2012; Staes et al., 2018; Issa et al., 2019), but very little is known about the genetic targets underlying these behavioral differences. For example, compared with chimpanzees, bonobos perform better on tasks related to understanding social causality or theory of mind (Herrmann et al., 2010) and receptive joint attention (Kano and Call, 2014; Hopkins et al., 2017), all indicators of higher empathic sensitivity, which is believed to be reflected in larger grey matter volumes of brain regions like the amygdala and insular cortex in bonobos (Hopkins et al., 2009; Rilling et al., 2012; Issa et al., 2019). In addition, studies in bonobos have described higher levels of between- and within-group social tolerance, cooperation and prosociality (Idani, 1990; Hare et al., 2007; Hare and Kwetuenda, 2010; Furuichi, 2011; Tan and Hare, 2013; but see; Cronin et al., 2015; Yamamoto, 2015; Yamamoto and Furuichi, 2017).

Genetic variation underlying within-species variation in sociocognitive skills has been well studied in humans (Skuse and Gallagher, 2011; Wilczyński et al., 2019). While sociocognitive abilities are influenced by a large number of genes, genes encoding receptors for neuropeptides and neurotransmitters, including oxytocin (*OXTR*), vasopressin (*AVPR1A*), dopamine (*DRD2*), and serotonin (*HTR1A*), appear to be particularly important in the regulation of social behavior (Skuse and Gallagher, 2011; Wilczyński et al., 2019). Oxytocin and vasopressin are neuropeptides that closely mediate social bonding and affect in mammals (for review, see Insel, 2010; Jurek and Neumann, 2018; Boender and Young, 2020). Neurons producing oxytocin (OT) and vasopressin (AVP) project from the supraoptic and paraventricular nuclei of the neurohypophyseal tract to mesolimbic and forebrain regions that are crucial for the processing of social information (Young and Gainer, 2003), and fibers containing OT and AVP have been identified in the cortex of humans, chimpanzees, and rhesus macaques (Rogers et al., 2018). OT and AVP mediate affiliative social relationships, social memory, empathy, prosociality, and anxiety (Insel, 2010) by modulating processes associated with reward and motivation, which are in turn regulated by the neurotransmitter dopamine (Nair and Young, 2006). The serotonergic system adds to the complexity of the social brain by regulating a wide range of functions like appetite and sleep, but also behavioral inhibition, which is in turn closely related to impulsive aggression, cooperativeness, and anxiety (reviewed in Skuse and Gallagher, 2011). The genes encoding the neuropeptides (OT and AVP), for example, show very little sequence variation (Ren et al., 2014; Babb et al., 2015), but the genes coding for the receptors are more variable and therefore better candidates to explain behavioral variation in these traits between- and within-species.

Polymorphisms in the receptor genes have been linked in humans to social sensitivity (empathy, mind reading, eye gazing, face perception, autism), prosociality (trust, altruism, generosity, betrayal aversion), social tolerance (aggressiveness, competition), and anxiety (for reviews, see Ebstein et al., 2010; Skuse and Gallagher, 2011; Walter, 2012; Wilczyński et al., 2019). While the exact mechanisms are not always known for each polymorphism, studies have documented links of genetic changes with altered gene expression, receptor distribution and/or receptor-ligand binding (Hammock and Young, 2005; Knafo et al., 2008; Hirvonen et al., 2009; King et al., 2016). Given the association of these genetic variants with sociocognitive skills in humans and the reported differences in these traits between humans and great apes, determining the extent of genetic sequence variation in these receptor genes between these species is of interest. It is also known that hominoids, including humans, show incomplete lineage sorting, so discerning whether genetic variants found in humans represent ancestral polymorphism that is shared with apes or is really human-specific can help us understand better their evolutionary history and potential functional impact (Scally et al., 2012). Such data can help us to uncover when in our evolutionary past key mutations arose and how they might have affected sociocognitive skills. Previous studies have taken a step in this direction by assaying known human polymorphic regions in other primates, including bonobos and chimpanzees, with a focus on regulatory microsatellites in the promoter region (Barr et al., 2004; Hopkins et al., 2012; Babb et al., 2015; Staes et al., 2015, 2016; Inoue-murayama et al., 2018). However, a limitation of most of these studies is their restriction to variants identified in human behavioral association studies. To obtain a more complete picture, a systematic screening for genetic variation in these genes in other ape species is warranted.

While many regulatory genetic and epigenetic mechanisms, like intronic variants, promoter region microsatellites, and methylation, are known to impact behavior through differential gene expression (Spielmann and Mundlos, 2016), we will first focus on variation in the protein coding region of the genes. Mutations that cause amino acid changes (nonsynonymous variants) have the potential to directly impact the structure and/or function of the receptor proteins through modification of ligand-binding affinity and signaling efficiency (Ren et al., 2014; Babb et al., 2015). Therefore, we first assess between-species variation in the coding regions of the four genes of interest in bonobos and chimpanzees. By comparing between-species variation in *Pan* with published sequences of humans, gorillas, orangutans, and gibbons, we can identify which variants are divergent from the other ape species and are therefore likely to underly behavioral differences, thereby reconstructing their evolutionary history. For nonsynonymous mutations, we investigate their potential impact on the structure and/or function of the receptor proteins. We also assess any history of signatures of selection on these genes using a d_N/d_S-based framework. d_N is the rate of nonsynonymous substitution per nonsynonymous site, or site within a protein that, if changed, could change the encoded amino acid at that codon. d_S is the rate of synonymous substitution per synonymous site (Yang and Nielsen, 2002). A synonymous mutation indicates a change in the DNA sequence that codes for amino acids in a protein sequence, but that does not change the encoded amino acid. The ratio of these two rates dn/ds accounts for substitution rate to reflect relative protein change, with an elevated d_N/d_S representing accelerated protein evolution. We also quantify within-species polymorphic variation in both species, which might be relevant for future studies investigating proximate origins of between- and within-species differences in behavior in bonobos and chimpanzees. Finally, we document all coordinates that show differences in both coding and noncoding regions of *Pan* sequences compared with the human reference sequences and further investigate their potential impact on between- and within-species behavioral differences. Especially for *OXTR* and *AVPR1A*, SNVs (single-nucleotide variants) in intronic and regulatory regions have been proven to play an important role in gene expression and behavioral regulation (Lerer et al., 2008; Israel et al., 2009; Rodrigues et al., 2009; Okhovat et al., 2015; King et al., 2016). To investigate the potential role of sequence differences in *Pan*, we will provide an extensive literature review of corresponding human SNVs that have documented links with behavioral traits and discuss their potential relevance.

2. Methods

2.1. Identifying between- and within-species genetic variation

To determine the interspecific variation in the coding sequences of our genes of interest, we used the Ensembl genome browser v. 69 (Yates et al., 2020) to extract coding sequences and their coordinates for *AVPR1A*, *OXTR*, *DRD2*, and *HTR1A* in humans (*Homo sapiens*, genome GRCh38), chimpanzees (*P. troglodytes*, genome Pan_tro_3.0), bonobos (*Pan paniscus*, genome panpan1.1), western lowland gorillas (*Gorilla gorilla gorilla*, genome gorGor4), Sumatran orangutans (*Pongo abelii*, genome PPYG2), and white-cheeked gibbons (*Nomascus leucogenys*, genome Nleu_3.0). We included rhesus macaques as an outgroup species (*Macaca mulatta*, genome Mmul_10). Sequences were aligned using Geneious v. 6.0.6 (Biomatters, San Diego). For individual Ensembl sequence reference numbers we refer to Supplementary Online Material (SOM) Table S1. Ensembl sequences for bonobos and chimpanzees were cross-checked for similarity with newer versions (Panpan3 and Clint_PTRv2/panTro6) for sequence identity, and we found minimal sequence differences that did not impact the results. For protein sequences, we calculated the percentage of pairwise identity by looking at all pairs of bases at the same column (across all species) and scoring a hit (one) when they are identical, divided by the total number of pairs. Ambiguity characters were interpreted, meaning a nucleotide A versus a nucleotide R is considered to have 50% identity. Identification of polymorphic variation within chimpanzees and bonobos was based on publicly available variant call format (VCF) files originating from whole genome and exome data (*Pan troglodytes troglodytes*, $n = 18$; *Pan troglodytes verus*, $n = 12$; *Pan troglodytes schweinfurthii*, $n = 16$; *Pan troglodytes ellioti*, $n = 10$; *Pan troglodytes* ssp. indet., $n = 3$; *Pan paniscus*, $n = 33$; Prado-Martinez et al., 2014; Teixeira et al., 2015; de Manuel et al., 2016). As VCF files were aligned to different reference genomes (either hg18 or hg19) depending on the study in which they were conducted, coordinates of SNVs were all transformed to coordinates in hg18 using the BLAT function in the UCSC genome browser (Kent, 2002) and cross-checked in the most recent human reference genome (hg38). As three different VCF data sets containing different sets of individuals were analyzed separately, rare variants often only occurred in one of the data sets. In these cases, genotype frequencies were based solely on those data sets where the mutations were present and thus the VCF output provided individual genotype information for all individuals in that data set at the position of the mutation. The sampled bonobos and chimpanzees in these studies were assumed to be unrelated, as they mostly consisted of wild-born individuals that ended up in captivity over a period of ~30 years and were sampled from populations spanning the entire geographical distribution of the two species throughout Africa (Reinartz et al., 2000; Eriksson et al., 2004; Van Coillie et al., 2008). The number of individuals exceeded 25 individuals for each species, ensuring a representative estimate of variation in populations (Hale et al., 2012).

2.2. Function and structure prediction of nonsynonymous variants

To infer the putative functional consequences of the identified coding variants, we first used SNAP2 to predict the effect of variants on protein function (Hecht et al., 2015). SNAP2 is a trained classifier that is based on a machine-learning device called 'neural network'. It distinguishes between effect and neutral variants/nonsynonymous SNVs by taking a variety of sequence and variant features into account. The effect of a variant is believed to be of importance to the native protein function and structure if the SNAP2 score exceeds 50; neutral if the score is below −50; and unreliable when between 50 and −50 (Hecht et al., 2015). SNAP2 results were verified using a different function prediction tool, PROVEAN (Choi and Chan, 2015), and no differences in outcome were found. To visualize the position of the coding variant in the protein sequence and accompanied functional domains of the receptor, we modelled the 2D structure of the transmembrane proteins using protter, a Web-based tool that supports interactive protein data analysis by visualizing annotated sequence features in the context of protein topology (Omasits et al., 2014). Using the 'HWAlltests' function in the HardyWeinberg package (Graffelman, 2015) in R v. 3.3.2 (R Core Team, 2017), we tested for population adherence to Hardy−Weinberg equilibrium per species, but only for SNVs where each genotype class contained a minimum of five individuals, as this is the minimum required for reliable calculation of Hardy−Weinberg equilibrium (Court, 2008).

Finally, to further identify potential functional implications of variants, we used a d_N/d_S-based framework to assess evidence for selection in the chimpanzee, bonobo, and ancestral *Pan* lineage for the four genes of interest. For each gene, we used orthologous sequence alignments of 30 mammals, including 27 primates (SOM, Table S2 from the University of California at Santa Cruz Genome Browser website; http://genome.ucsc.edu/cgi-bin/hgTrackUi?db=hg38&g=cons30way) and a species tree (SOM Fig. S1). The consensus species tree was downloaded from the 10KTrees website (Arnold et al., 2010). The topology of this tree was concordant with a more recently published primate phylogeny estimated using genomic-scale data (Reis et al., 2018). We then added the outgroup species in a way consistent with accepted mammalian taxonomy (Kumar et al., 2017). We estimated branch and branch-site d_N/d_S on three branches of interested (chimpanzees, bonobos, and the ancestral *Pan* branch) under positive selection and neutral evolution models using codeml (Yang, 2007) within the Python wrapper ete3 (Huerta-Cepas et al., 2016). Branch models estimate d_N/d_S across an entire gene sequence, whereas branch-sites models allow d_N/d_S to vary across sites and lineages simultaneously such that elevated d_N/d_S may be identified at specific sites on particular branches. We then applied likelihood ratio tests (LRTs) to determine whether a model of positive selection was

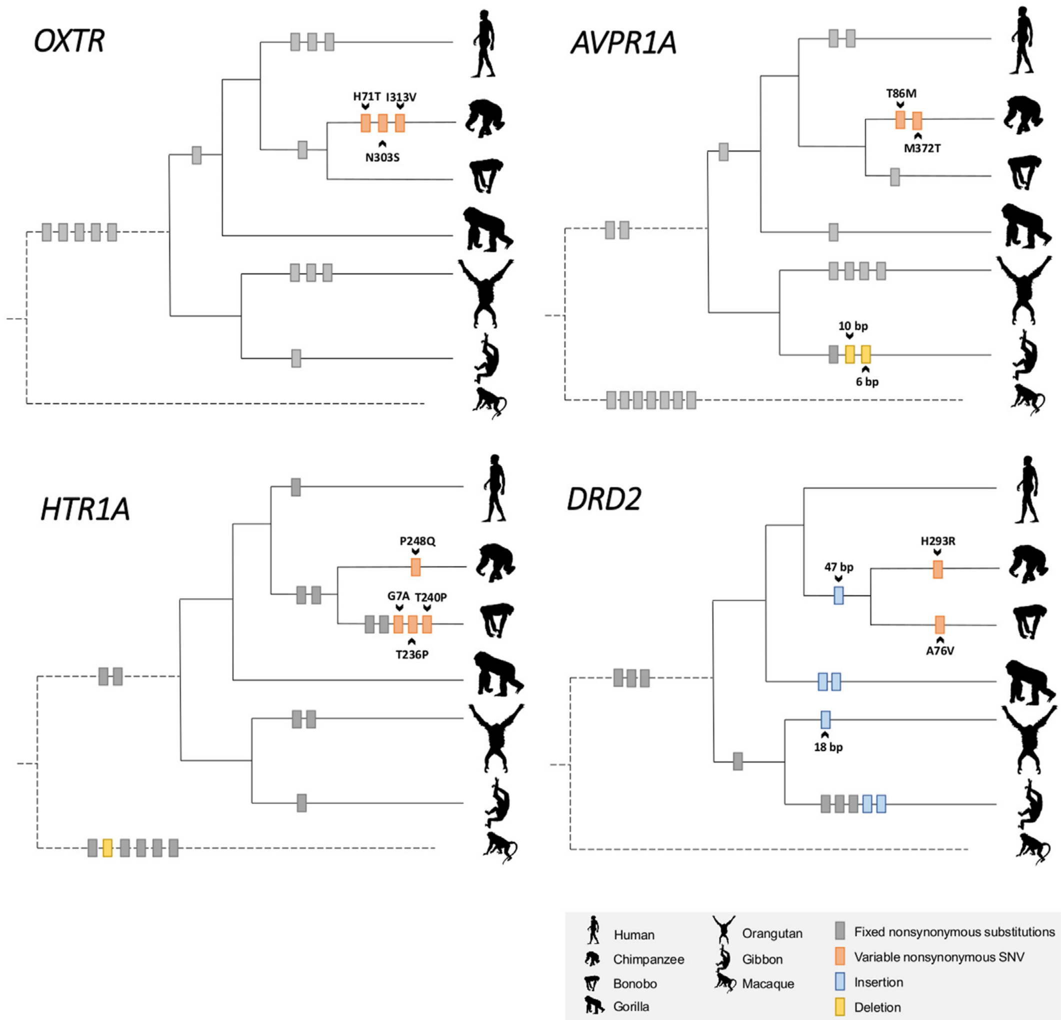

Figure 1. Coding sequence variation in six species of Hominoidea, with macaques as an outgroup species. Fixed amino acid changes are indicated in gray. For chimpanzees and bonobos polymorphic within-species nonsynonymous variation is also shown (in orange) and amino acid substitutions and their positions are indicated. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

significantly better than the null model of neutral evolution, using a *p*-value threshold of 0.05 (SOM Table S3). We first estimated locus-specific branch lengths for each gene from the number of nucleotide substitutions per codon under a null model of a single rate of substitution across the tree (codeml model M0) and used these branch lengths in subsequent analyses.

2.3. Behavioral function of sequence differences in Pan versus humans

Finally, for all positions where the *Pan* sequences differed from the human reference sequence in both coding and noncoding regions of the genes, we assessed their potential associations with sociocognitive traits. To do so, we compared allelic changes in *Pan* to known human SNVs that have been linked to behavioral traits. We identified human SNVs using the Ensembl variant tables (Yates et al., 2020) for each gene, which contain all variants previously identified in the 1000 genomes project (The 1000 genomes project consortium, 2015) for a region spanning 5 kb upstream and downstream of the gene. Next, we filtered out all SNVs that have been documented in literature, indicated as 'cited' in the table and matched their coordinates in *Pan* to human hg38 coordinates used in the variant tables with the BLAT tool of the UCSC genome browser (Kent, 2002). For each SNV we then did an extensive literature review using the dbSNP database (Sherry et al., 2001) to assess precise human-specific documented links with different phenotypic traits and highlighted those SNVs that have been linked to behavioral phenotypes (Table 4).

3. Results

3.1. OXTR

Between-species The amino acid coding sequence for the oxytocin receptor gene showed high stability across ape species, with 98.7% pairwise identity (SOM Fig. S2). The human sequence showed three fixed amino acid changes (V14A, F51L, and K355R) in comparison with other apes, including bonobos and chimpanzees (Fig. 1). Bonobos and chimpanzees shared one amino acid substitution with each other that differed from all other apes (K353R) but did not

Table 1
SNAP2 function prediction scores for amino acid (AA) substitutions in humans and *Pan*.[a]

Gene	Species	AA change	Effect	Strength	Reliability	Variable
OXTR	*Homo sapiens*	V14A	Neutral	−10	53%	Fixed
	Homo sapiens	**F51L**	**Neutral**	**−51**	**66%**	**Fixed**
	Pan troglodytes	H71T	Neutral	−34	66%	SNV
	Pan troglodytes	**N303S**	**Neutral**	**−81**	**93%**	**SNV**
	Pan troglodytes	I313V	Neutral	−47	72%	SNV
	Pan[b]	**K353R**	**Neutral**	**−83**	**93%**	**Fixed**
	Homo sapiens	**K355R**	**Neutral**	**−88**	**93%**	**Fixed**
AVPR1A	*Pan paniscus*	G29S	Neutral	−46	72%	Fixed
	Pan troglodytes	T86M	Neutral	−40	66%	SNV
	Homo sapiens	R248C	Effect	33	66%	Fixed
	Homo sapiens	**K322M**	**Neutral**	**−82**	**93%**	**Fixed**
	Pan troglodytes	M372T	Effect	9	53%	SNV
DRD2	***Pan paniscus***	**A76V**	**Neutral**	**−70**	**82%**	**SNV**
	Pan troglodytes	H293R	Effect	15	59%	SNV
HTR1A	*Pan paniscus*	G7A	Neutral	−18	57%	SNV
	Pan[b]	**T22S**	**Neutral**	**−94**	**97%**	**Fixed**
	Homo sapiens	**F33V**	**Neutral**	**−60**	**78%**	**Fixed**
	Pan paniscus	T236P	Neutral	−41	72%	SNV
	Pan paniscus	T240P	Neutral	−43	72%	SNV
	Pan[b]	P248Q	Neutral	−25	61%	fixed/SNV
	Pan paniscus	**E267D**	**Neutral**	**−76**	**87%**	**Fixed**
	Pan paniscus	H296Y	Neutral	−34	66%	Fixed

[a] Boldface indicates reliable estimates (>50 or < −50).
[b] '*Pan*' indicates that the substitution is present in both *Pan* species.

Table 2
Results of the d_N/d_S-based selection analysis.

	Branch models						Branch-sites models					
	Chimpanzee		Bonobo		Ancestral *Pan*		Chimpanzee		Bonobo		Ancestral *Pan*	
Gene	d_N/d_S	LRT *p*	d_N/d_S	LRT *p*	d_N/d_S	LRT *p*	PSS	LRT *p*	PSS	LRT *p*	PSS	LRT *p*
OXTR	0.56	1.00	0.00	0.99	999.00	0.10	–	1.00	–	1.00	K353R	0.59
AVPR1A	0.00	0.35	0.23	0.68	0.00	0.06	–	0.99	G26S	1.00	–	1.00
DRD2	0.58	0.99	0.00	0.40	0.00	0.40	–	1.00	–	1.00	–	1.00
HTR1A	0.56	0.99	0.25	0.21	999.00	0.01*	–	1.00	E268D, H296Y	1.00	–	0.35

Abbreviations: PSS = positively selected sites; LRT = likelihood-ratio test; dN/dS = ratio of number of nonsynonymous substitutions per non-synonymous site to number of synonymous substitutions per synonymous site.
* indicates significant at treshold p < 0.05.

show any other fixed differences within either species. Two-dimensional structure prediction showed that human V14A, F51L, and K355R were located at the N-terminal region, transmembrane region and intracellular C-terminus, respectively (SOM Fig. S3). Similar to K355R, *Pan* K353R was present in the C-terminal region. SNAP2 function prediction analysis revealed a likely neutral effect for three amino acid changes (F51L: strength −51, reliability 66%; K353R: strength −83, reliability 93%; K355R: strength −88, reliability 93%) but failed to reliably predict functionality of human V14A (Table 1). Finally, evolutionary modelling analysis failed to show signatures of selection in *OXTR* in either the human or *Pan* lineages, as none of the branch or branch-site models were significantly better than the null model (Table 2).

Within-species Within-species comparison revealed eight polymorphic sites in *Pan*: two synonymous SNVs in bonobos, and three synonymous and three nonsynonymous variants (H71T, N303S, I313V) in chimpanzees (Table 3). Minor allele frequencies (MAFs) were low for all three nonsynonymous variants: H71T: MAF T = 0.009, N303S: MAF G = 0.025, I313V: MAF G = 0.008. Two-dimensional structure prediction showed that chimpanzee H71T is located in the first intracellular loop, N303S in the third extracellular loop and I313V in the seventh transmembrane region (SOM Fig. S3). SNAP2 function prediction analysis revealed a likely neutral effect for N303S in chimpanzees (strength −81, reliability 93%) but failed to reliably predict functionality of the other two amino acid changes (Table 1).

Behavioral function In those cases where either one or both *Pan* *OXTR* sequences differed from the human reference sequence, we identified a total of 17 coordinates where SNVs with documented phenotypic links in humans were present (Table 4). These SNVs were linked to a wide range of behavioral phenotypes including anxiety, aggression, social bonding, social memory, emotion recognition, and prosociality (for references see Table 4). Only 3 of the 17 SNVs showed genotype differences between bonobos and chimpanzees, while the remaining 13 SNVs only showed allelic variation in humans but were identical in bonobos and chimpanzees. First, rs4686301 is an intronic T > C substitution in humans (MAF T = 0.264) where the C allele is considered a risk allele for autism (Lerer et al., 2008). At this position, humans share the T allele with bonobos, who are all homozygous TT, whereas chimpanzees are all homozygous for the C allele. Second, rs237897 is an intronic G > A substitution in humans (MAF A = 0.402), where the A allele is linked to better theory of mind (Wade et al., 2015), stronger response to betrayal (Tabak et al., 2014), and male prosociality (Israel et al., 2009). At this position, all bonobos have the human-specific A allele, whereas chimpanzees have the ancestral GG genotype. Finally, rs2228485 is a synonymous A > G substitution, present in exon 3 (MAF G = 0.282). The A allele has been linked to a better ability to read emotional responses in male faces and humans share this allele with all chimpanzees, whereas in bonobos the A allele is lacking.

Table 3
Single-nucleotide variants in *Pan* for four genes of interest compared with human genome hg18.

Gene	Exon	Coordinate[a]	Mutation	AA	Genotype distribution	Species
OXTR	1	chr3:8784663	C/T	H71T	C/C: 53 (98.11%); C/T: 1 (1.89%)	*Pan troglodytes*
	1	chr3:8784163	A/G	—	A/A: 44 (84.61%); A/G: 3 (5.77%); G/G: 5 (9.62%)	*Pan troglodytes*
	1	chr3:8783966	A/G	N303S	A/A: 57 (95.00%); A/G: 3 (5.00%)	*Pan troglodytes*
	1	chr3:8783965	C/T	—	C/C: 8 (61.54%); C/T: 4 (30.67%); T/T:1 (7.69%)	*Pan paniscus*
	2	chr3:8769906	G/A	—	G/G: 57 (95.00%); G/A: 3 (5.00%)	*Pan troglodytes*
	2	chr3:8769896	A/G	I313V	A/A: 59 (98.33%); A/G: 1 (1.67%)	*Pan troglodytes*
	2	chr3:8769729	G/A	—	G/G: 58 (98.31%); G/A: 1 (1.70%)	*Pan troglodytes*
	2	chr3:8769726	C/T	—	C/C: 11 (91.67%); C/T: 1 (8.33%)	*Pan paniscus*
AVPR1A	1	chr12:61830636	C/T	T86M	C/C: 54 (98.18%); C/T: 1 (1.81%)	*Pan troglodytes*
	1	chr12:61830476	T/C	—	T/C: 1 (5.56%); C/C: 17 (94.4%)	*Pan paniscus*
	2	chr12:61827557	T/C	M372T	T/T: 54 (90.00%); T/C: 4 (6.67%); C/C: 2 (3.33%)	*Pan troglodytes*
	2	chr12:61827535	A/G	—	A/A: 16 (80%); A/G: 4 (20%)	*Pan paniscus*
	2	chr12:61827469	G/C	—	G/G: 59 (98.33%); G/C: 1 (1.67%)	*Pan troglodytes*
	2	chr12:61827457	G/A	—	G/G: 12 (92.31%); G/A: 1 (7.69%)	*Pan paniscus*
DRD2	1	chr11:112800515	G/A	—	G/G: 56 (94.92%); G/A: 2 (3.39%); A/A: 1 (1.70%)	*Pan troglodytes*
	1	chr11:112800498	G/A	A76V	G/G: 20 (60.61%); G/A: 11 (33.33%); A/A: 2 (6.06%)	*Pan paniscus*
	1	chr11:112800434	G/A	—	G/G: 59 (98.33%); G/A: 1 (1.67%)	*Pan troglodytes*
	1	chr11:112800335	G/A	—	G/G: 59 (98.33%); G/A: 1 (1.67%)	*Pan troglodytes*
	2	chr11:112794000	G/A	—	G/G: 58 (96.77%); G/A: 2 (3.33%)	*Pan troglodytes*
	3	chr11:112792895	C/T	—	C/C: 58 (96.77%); C/T: 2 (3.33%)	*Pan troglodytes*
	4	chr11:112791371	G/A	—	G/G: 59 (98.33%); G/A: 1 (1.67%)	*Pan troglodytes*
	5	chr11:112790380	T/C	H293R	T/T: 59 (98.33%); T/C: 1 (1.67%)	*Pan troglodytes*
	6	chr11:112788669	G/A	—	G/G: 59 (98.33%); A/A: 1 (1.67%)	*Pan troglodytes*
	7	chr11:112786731	G/A	—	G/G: 58 (96.77%); G/A: 2 (3.33%)	*Pan troglodytes*
HTR1A	1	chr5:63293240	C/A	—	C/C: 59 (98.33%); C/A: 1 (1.67%)	*Pan troglodytes*
	1	chr5:63293226	C/G	G7A	C/G: 1 (3.03%); G/G: 32 (96.96%)	*Pan paniscus*
	1	chr5:63293087	T/C	—	T/T: 58 (96.77%); T/C: 2 (3.33%)	*Pan troglodytes*
	1	chr5:63292982	A/C	—	A/C: 1 (3.03%); C/C: 32 (96.96%)	*Pan paniscus*
	1	chr5:63292934	C/T	—	C/C: 59 (98.33%); C/T: 1 (1.67%)	*Pan troglodytes*
	1	chr5:63292922	G/C	—	G/G: 12 (92.31%); G/C: 1 (7.69%)	*Pan paniscus*
	1	chr5:63292808	C/T	—	C/C: 15 (75%); C/T: 5 (25%)	*Pan paniscus*
	1	chr5:63292613	C/A	—	C/C: 14 (70%); C/A: 6 (30%)	*Pan paniscus*
	1	chr5:63292601	G/A	—	G/G: 19 (95%); G/A: 1 (5%)	*Pan paniscus*
	1	chr5:63292597	A/C	T236P	A/A: 18 (90%); A/C: 2 (10%)	*Pan paniscus*
	1	chr5:63292589	G/T	—	G/G: 26 (78.78%); G/T: 6 (18.18%); T/T: 1 (3.03%)	*Pan paniscus*
	1	chr5:63292585	A/C	T240P	A/A: 7 (35%), A/C: 13 (65%)	*Pan paniscus*
	1	chr5:63292560	C/A	P248Q	C/A: 4 (6.66%); A/A: 56 (93.33%)	*Pan troglodytes*
	1	chr5:63292529	G/A	—	G/G: 56 (93.33%); G/A: 4 (6.66%)	*Pan troglodytes*

Abbreviation: AA = amino acid change.
[a] Coordinates indicate position in hg18 of University of California Santa Cruz genome browser.

3.2. AVPR1A

Between-species The AVPR1A protein sequence showed 97.5% pairwise identity, indicating high stability across species (SOM Fig. S4). The human sequence showed two fixed nonsynonymous changes (R248C and K322M) relative to all other ape species (Fig. 1), which are located in the third intracellular loop and the third extracellular loop, respectively (SOM Fig. A5). The bonobo lineage further showed one fixed amino acid substitution (G29S) at the extracellular N-terminus, while no chimpanzee-specific fixed changes are present. SNAP2 function prediction analysis revealed a likely neutral effect for human K322M (strength −82, reliability 93%) but failed to reliably predict functionality of the other fixed amino acid changes (Table 1). Evolutionary modelling revealed no clear signatures of selection in *AVPR1A* in human or *Pan* lineages, as none of the branch or branch-site models were significantly better than the null model (Table 2).

Within-species Within-species comparison in *Pan* revealed 6 polymorphic sites: three synonymous SNVs in bonobos, and one synonymous and two nonsynonymous variants (T86M, M372T) in chimpanzees (Table 3). For both nonsynonymous variants, the minor alleles are present at relatively low frequencies in the population (T86M: MAF T = 0.009, M372T: MAF C = 0.067). Two-dimensional structure prediction showed that chimpanzee T86M is located in the first intracellular loop and M372T in the C-terminal region (SOM Fig. A5), but SNAP2 functional analysis failed to reliably estimate potential differences in functionality for either amino acid change (Table 1).

Behavioral function For *AVPR1A*, only one coordinate matched a documented human SNV, rs10747983, but there was no known link with behavioral phenotypes.

3.3. DRD2

Between-species The DRD2 amino acid coding sequence showed 99.2% pairwise identity across species (SOM Fig. S6). Humans showed no fixed amino acid differences with other apes, but both *Pan* species showed an identical 141bp insertion right at the start codon, resulting in an additional 47 amino acids at the N-terminal region of the receptor (Fig. 2). The lack of amino acid variation in humans and *Pan* is reflected in the results of the evolutionary modelling, where no signatures of selection were found (Table 2).

Within-species Within-species comparison revealed 10 polymorphic sites in *Pan*: one nonsynonymous SNV (A76V) in bonobos, and eight synonymous SNVs and one nonsynonymous SNV (H293R) in chimpanzees (Table 3). For bonobo A76V, the MAF is relatively high in the population (MAF A = 0.227), and genotype frequencies are consistent with Hardy–Weinberg equilibrium ($X^2 = 0.09$, df = 1, $p = 0.769$). This variant is present in the extracellular N-terminal region (SOM Fig. S7), and SNAP2 function prediction analysis revealed a likely neutral effect (strength −70, reliability 82%; Table 1). Chimpanzee H293R is rare in the

Table 4
Overview of human single-nucleotide variants with references to behavioral consequences and respective alleles in *Pan*.

Gene	Variant ID	Type of SNV	Allele_anc/ allele_alt	human gmaf freq	# Cited	Links to behavior	Reference	Present in	*Pan* gmaf freq
OXTR	rs6770632	3 prime UTR variant	A/C	A (0.226)	6	A risk allele female aggression	Malik et al. (2012)	*Pan*	A (1.000)
						G risk allele male aggression	Malik et al. (2012)		
	rs1042778	3 prime UTR variant	A/T	T (0.411)	48	TT lower marital quality	Mattson et al. (2019)	*Pan*	T (1.000)
						TT lower maternal acceptance	Savelieva et al. (2019)		
						TT higher anxiety	Julian et al. (2019)		
						T lower prosociality	Israel et al. (2009)		
	rs237885	Intron variant	G/T	G (0.488)	15	TT higher aggression	Zhang et al. (2018b)	*Pan*	G (1.000)
	rs237887	Intron variant	A/G	G (0.400)	34	A allele antisocial behavior	Poore and Waldman (2020)	*Pan*	A (1.000)
						A risk allele autism	LoParo and Waldman (2015)		
						A allele impaired social memory	Skuse et al. (2014)		
						GG higher empathy, prosociality	Wu et al. (2012)		
	rs237888	Intron variant	C/T	C (0.125)	3	T allele impaired joint attention	Wilczyński et al. (2019)	*Pan*	C (1.000)
						C allele less prosocial	Israel et al. (2009)		
	rs4686301	Intron variant	T/C	T (0.264)	9	C risk allele autism IQ (haplotype)	Lerer et al. (2008)	*Pan paniscus*	T (1.000)
	rs237889	Intron variant	C/T	T (0.300)	13	C more utilitarian response	Bernhard et al. (2016)	*Pan*	C (1.000)
						T risk allele autism	Kranz et al. (2016)		
	rs59190448	Intron variant	A/G	A (0.136)	1	G risk allele anxiety, stress	Myers et al. (2014)	*Pan*	A (1.000)
	rs53576	Intron variant	G/A	A (0.389)	184	A allele lower empathy, more stress	Rodrigues et al. (2009)	*Pan*	G (1.000)
						GG lower empathy	Laursen et al. (2014)		
						A allele reduced maternal sensitivity	Riem et al. (2011)		
						G allele greater sociality	Li et al. (2015)		
						AA reduced non-verbal intelligence	Lucht et al. (2009)		
	rs237895	Intron variant	C/T	T (0.397)	2	T risk allele maternal insensitivity	Toepfer et al. (2019)	*Pan*	C (1.000)
	rs2268495	Intron variant	A/G	A (0.241)	2	G risk allele autism	Xiaoxi et al. (2010)	*Pan*	A (1.000)
	rs2268496	Intron variant	A/T	A (0.251)	1	None		*Pan*	A (1.000)
	rs237897	Intron variant	G/A	A (0.402)	15	A better theory of mind – haplotype	Wade et al. (2015)	*Pan troglodytes*	G (1.000)
						A stronger response to betrayal	Tabak et al. (2014)	*Pan paniscus*	A (1.000)
						A male prosociality	Israel et al. (2009)		
						A risk allele autism-haplotype	Lerer et al. (2008)		
	rs2228485	Synonymous variant	A/G	G (0.282)	9	A better at mind-reading	Lucht et al. (2013)	*Pan troglodytes*	A (1.000)
						A allele less emotional loneliness	Lucht et al. (2009)	*Pan paniscus*	G (1.000)
	rs237911	5 prime UTR variant	A/G	G (0.140)	3	A risk allele autism	Wu et al. (2005)	*Pan*	A (1.000)
	rs4564970	Intron variant	A/C	C (0.137)	8	C risk allele aggression	Johansson et al. (2012)	*Pan*	C (1.000)
AVPR1A	rs10747983	3 prime UTR variant	A/G	A (0.316)	1	None	None	*Pan*	A (1.000)
DRD2	rs2734841	Intron variant	C/A	A (0.453)	1	None	None	*Pan*	C (1.000)
	rs1124493	Intron variant	G/T	T (0.478)	4	None	None	*Pan*	G (1.000)
	rs6277	Synonymous variant	A/G	A (0.244)	133	G risk allele schizophrenia	Sakurai et al. (2012)	*Pan troglodytes*	A (0.040)
						A risk allele inhibition impulse control	Della Torre et al. (2018)		
						GG increased reward-related memory	Richter et al. (2017)		
	rs6275	Synonymous variant	G/A	A (0.473)	49	AA increased risk schizophrenia	Nkam et al. (2017)	*Pan*	G (1.000)
	rs12363125	Intron variant	T/C	T (0.276)	5	None	None	*Pan*	T (1.000)
	rs2734839	Intron variant	A/T	T (0.342)	2	AA increased risk schizophrenia	Voisey et al. (2012)	*Pan*	T (1.000)
	rs2734837	Intron variant	T/C	T (0.342)	2	None	None	*Pan*	T (1.000)
	rs2440390	Intron variant	C/T	T (0.116)	1	None	None	*Pan*	C (1.000)
	rs2245805	Intron variant	G/T	T (0.421)	1	G risk allele addiction	Zhang et al. (2018a)	*Pan*	G (1.000)
	rs2734836	Intron variant	T/C	T (0.228)	5	None	None	*Pan*	T (1.000)
	rs1076563	Intron variant	C/A	C (0.293)	7	None	None	*Pan*	C (1.000)
	rs1076562	Intron variant	G/A	A (0.422)	6	None	None	*Pan*	G (1.000)
	rs1125394	Intron variant	C/T	C (0.265)	17	T risk allele addiction	Al-eitan et al. (2012)	*Pan*	C (1.000)
						T risk allele depression	Hamidovic et al. (2010)		
	rs7103679	Intron variant	C/T	T (0.214)	6	None	None	*Pan*	C (1.000)
	rs4648319	Intron variant	A/T	A (0.208)	5	T risk allele addiction	Chang-Chih et al. (2019)	*Pan*	A (1.000)
						Creative potential	Zhang et al. (2014)		
	rs4245147	Intron variant	G/C or T	C (0.455)	3	None	None	*Pan*	T (1.000)
	rs4936270	Intron variant	C/T	T (0.250)	1	Addiction	Loughlin et al. (2014)	*Pan*	C (1.000)
	rs4936271	Intron variant	C/T	T (0.435)	1	Addiction	Celorrio et al. (2016)	*Pan*	C (1.000)
	rs4936272	Intron variant	C/T	T (0.435)	1	None	None	*Pan*	C (1.000)

(*continued on next page*)

Table 4 (*continued*)

Gene	Variant ID	Type of SNV	Allele_anc/ allele_alt	human gmaf freq	# Cited	Links to behavior	Reference	Present in	*Pan* gmaf freq
	rs4274224	Intron variant	A/G	G (0.449)	14	AA lower openness to experience GG higher risk depression	Peciña et al. (2013) Nyman et al. (2011)	*Pan*	A (1.000)
	rs77195172	Intron variant	T/C	T (0.053)	1	None	None	*Pan*	T (1.000)
	rs4245148	Intron variant	C/T	T (0.247)	4	C risk allele addiction	Liu et al. (2020)	*Pan*	C (1.000)
	rs4581480	Intron variant	T/C	C (0.247)	10	T risk allele addiction C risk allele reward and emotional processing	Li et al. (2015) Peciña et al. (2013)	*Pan*	T (1.000)
	rs7131056	Intron variant	C/A	C (0.499)	19	A risk allele depression A risk allele PTSD A risk allele social phobia	He et al. (2019) Duan et al. (2015) Sipilä et al. (2010)	*Pan*	C (1.000)
	rs11214613	Intron variant	G/A	A (0.243)	3	A risk allele addiction	Wei et al. (2012)	*Pan paniscus*	G (1.000)
	rs12421616	Intron variant	A/T	T (0.128)	1	None	None	*Pan*	A (1.000)
	rs1799978	Non-coding transcript variant	C/T	C (0.119)	32	C risk allele addiction	Bawor et al. (2015)	*Pan*	C (1.000)
HTR1A	rs749099	3 prime UTR variant	T/C	C (0.352)	1	None	None	*Pan*	T (1.000)
	rs878567	3 prime UTR variant	C/A	A (0.352)	24	A risk allele depression G risk allele schizophrenia A risk allele anxiety/depression	Kanders et al. (2020) Guan et al. (2016) Mekli et al. (2011)	*Pan*	G (1.000)
	rs6449693	3 prime UTR variant	A/G	G (0.351)	4	None	None	*Pan*	A (1.000)

Abbreviations: SNV = single-nucleotide variant; Allele_anc = ancestral allele; Allele_alt = alternative allele; gmaf freq = genotype minor allele frequency; UTR = untranslated region.

population and present in just one individual (MAF C = 0.008). Two-dimensional structure prediction showed that the variant is located in the third intracellular loop (SOM Fig. S7), but function prediction analysis could not reliably estimate its functionality (Table 1).

Behavioral function A total of 29 documented human SNVs were found to match differences in the *Pan*-human reference sequences for *DRD2* (Table 4), but for only 2 out of 29 SNVs, a difference in genotype or allele presence was found between the two *Pan* species. The remaining 27 SNVs thus showed identical fixed genotypes in both *Pan* species while they showed polymorphic variation in humans. The first SNV, rs6277, is a synonymous A > G substitution present in humans (MAF A = 0.244) and chimpanzees (MAF A = 0.040), but not in bonobos, who are all GG at this position. The A allele is linked to reduced impulse control (Della Torre et al., 2018) and reward-related memory (Richter et al., 2017). The second SNV, rs11214613, is an intronic G < A substitution (MAF A = 0.243) in humans. The A allele is linked to increased risk for addiction (Wei et al., 2012), and while chimpanzees all have the ancestral AA genotype, bonobos are all GG at this position.

3.4. HTR1A

Between-species The *HTR1A* amino acid coding sequence showed 96.2% pairwise identity across species (SOM Fig. S8). Humans showed one fixed amino acid change (F33V) from all other apes,

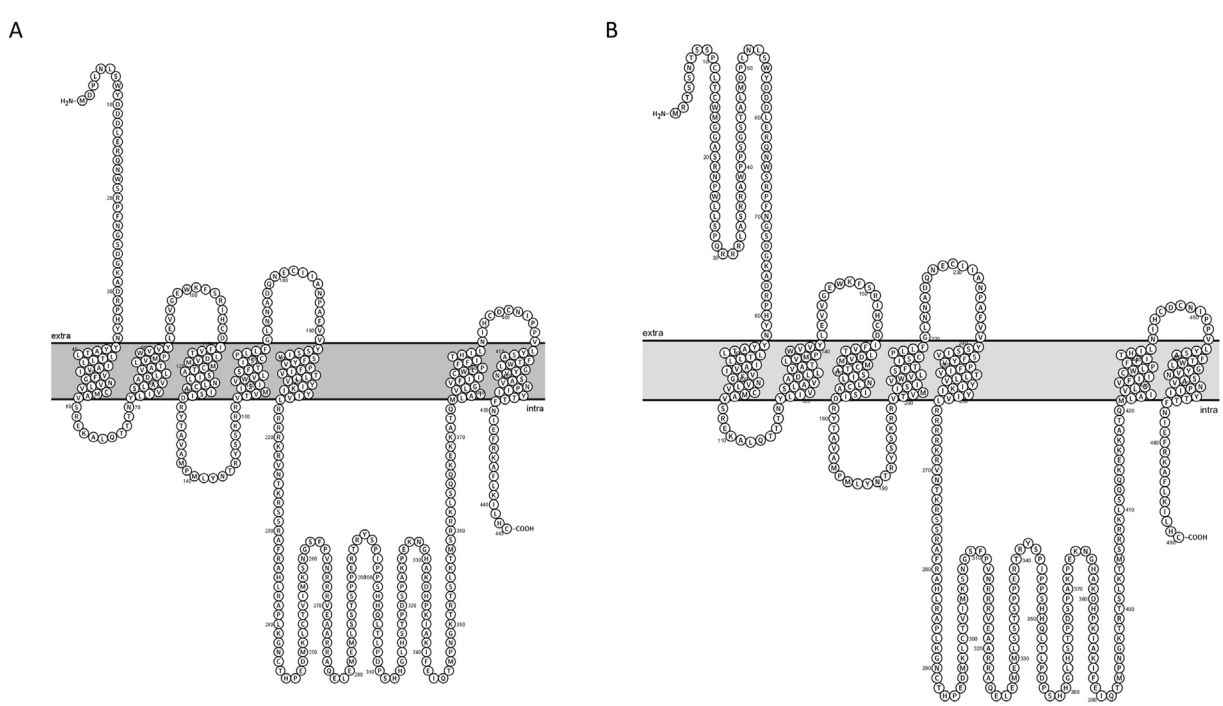

Figure 2. Two-dimensional structure prediction for DRD2: A) human DRD2 receptor; B) *Pan* DRD2 receptor with 47 amino acid insertion at N-terminal region.

present in the extracellular N-terminal region (SOM Fig. S9) and predicted to have a neutral effect (strength −60, reliability 97%; Table 1). Compared with other apes, chimpanzees and bonobos showed two *Pan*-specific changes (T26S and P248Q). While P248Q is fixed in bonobos, it is polymorphic in chimpanzees. T26S is also present in the N-terminal region (SOM Fig. S9) and is predicted to have a neutral effect (strength −94, reliability 97%; Table 1). P248Q is present in the third intracellular loop (SOM Fig. S9) but has an unreliable functionality estimate (Table 1). Finally, two bonobo-specific changes were present (E267D and H296Y), both in the third intracellular loop (SOM Fig. A9). SNAP2 function prediction analysis revealed a likely neutral effect for E267D (strength −76, reliability 87%) but failed to predict functionality of H296Y (Table 1). Evolutionary modelling revealed an elevated d_N/d_S ratio in the ancestral *Pan* lineage ($p = 0.013$) but omega equaled 999, indicating this is likely due to a lack of synonymous sites in the sequence. These results should therefore be treated with caution (Table 2).

Within-species Within-species comparison revealed 14 polymorphic sites in *Pan*: six synonymous and three nonsynonymous (G7A, T236P, T240P) SNVs in bonobos, and eight synonymous and one nonsynonymous SNVs (P248Q) in chimpanzees (Table 3). MAFs were low for three out of four SNVs found in *Pan* (G7A: MAF G = 0.015; T236: MAF G = 0.05; P248Q: MAF G = 0.033) but was considerably higher for bonobo T240P (MAF G = 0.175). Despite this relatively high frequency of the minor allele, no homozygotes for the minor allele were present in the population. Two-dimensional structure prediction shows that G7A is located in the extracellular N-terminus, while the other three SNVs are all located in the third intracellular loop (SOM Fig. S9). SNAP2 analysis could not reliably estimate functionality effect scores for any of the amino acid changes (Table 1).

Behavioral function For *HTR1A*, no sequence differences in *Pan* were found to match known human-specific SNVs with linked behavioral phenotypes.

4. Discussion

The main aim of this study was to investigate the evolutionary history of four genes important for the regulation of sociocognitive skills (*OXTR*, *AVPR1A*, *DRD2*, *HTR1A*) in the human and *Pan* lineages. Results showed that the protein coding sequences of all four genes are highly conserved across apes, in line with their close phylogenetic relationships (Besenbacher et al., 2019). We found a limited number of amino acid differences between species, which indicates that the sequences are likely under strong selection to maintain the anatomical and chemical properties of the receptor to ensure proper neuropeptide and neurotransmitter signaling. For variants outside of the coding region, we find considerable variation in all three species for all four genes. The most promising explanatory variants were present in *OXTR* and *DRD2*. We found interesting evidence of homologous evolution in humans and bonobos (*OXTR* rs4686301(T) and *OXTR* rs237897(A)) to the exclusion of chimpanzees. By contrast, humans and chimpanzees shared *OXTR* rs2228485(A), *DRD2* rs6277(A), and *DRD2* rs11214613(A), whereas bonobos maintained the ancestral state in all three cases.

4.1. Protein-coding region

While no fixed human-specific amino acid differences were found in DRD2 compared with other hominoids, six fixed amino acid changes were present in the remaining three genes in humans: three in *OXTR* (V14A, F51L, K355R), two in *AVPR1A* (R248C, K322M) and one in *HTR1A* (F33V). The protein sequences of the *Pan* lineage differed from humans and other apes in three additional sites, one in OXTR (K353R) and two in HTR1A (T22S and P248Q). Compared with chimpanzees, bonobos showed 57% more fixed differences, counting four additional fixed amino acid changes, three in HTR1A (E267D, P248Q and H296Y) and one in AVPR1a (G29S). For OXTR and DRD2, chimpanzees and bonobos showed no fixed differences with each other.

SNAP2 function prediction analysis showed that the amino acid changes likely do not significantly alter the chemical properties and 2D structure of the proteins. Nevertheless, the substitutions are found in functional domains of the receptors that are of great importance for the signaling function of the receptors (Kristiaensen, 2004). One of the bonobo-specific amino acid substitutions in AVPR1A (G29S) falls within the extracellular N-terminus, which is the major vasopressin ligand recognition and binding region of this receptor (Kristiaensen, 2004). Mutations in this region thus have the potential to cause differences in receptor binding sensitivity and have been identified in various New World monkey species (Babb et al., 2010; Ren et al., 2014) and non-primate species like voles (genus *Microtus*; Fink et al., 2007). Similarly, bonobos and chimpanzees share a 47 amino acid insertion at the N-terminal region of DRD2 that is not present in other apes. This *Pan*-specific insertion is very likely to cause differences in dopamine binding affinity, but functionality would need to be tested using experimental assays.

HTR1A substitutions E267D, P248Q, and H296Y are all present in the third intracellular loop of the receptor. The receptors included in this study are all G-protein-coupled receptors that typically have seven transmembrane alpha helices, which create three extracellular and three intracellular loops (Kristiaensen, 2004). The third intracellular loop is where each receptor couples to heterotrimeric G-proteins and intracellular second messengers like calmodulin to function in signal transduction (Turner et al., 2004; Masson et al., 2012). Mutations in this region thus have the potential to alter serotonergic functioning through a variety of potential intracellular signaling pathways. As we cannot directly infer behavioral consequences of these species-specific fixed mutations, functional assays would be needed to test their impact on ligand binding and signal transduction.

Overall, the level of genetic nonsynonymous variation was similar for all four genes across different ape species, with the exception of *HTR1A*. The high number of amino acid changes in HTR1A in ancestral *Pan* ($n = 2$) and bonobos specifically ($n = 4$) is surprising, given the low number of protein sequence changes in the other species (humans, $n = 1$; orangutans, $n = 2$; gibbons, $n = 2$; see SOM Fig. S8) and in the other genes. This result indicates that the serotonergic system was likely the target of selective pressures in *Pan*, which is also reflected in a high d_N/d_S score found in the ancestral *Pan* branch compared with the other branches, indicating positive selection. As mentioned, no synonymous substitutions were present in the sequence, so this result should be treated with caution. Nonetheless, the relatively high level of protein divergence between bonobos and chimpanzees very likely coincided with changes in serotonergic signaling and associated behavioral regulation. Previous studies have suggested that selective pressures for reduced aggression in bonobos might have been a major factor in driving the behavioral divergence in *Pan* (Hare et al., 2012; Hare, 2017). The genes coding for the serotonergic system are great candidate targets for selection to act on due to their significant role in the regulation of aggression (Hare et al., 2012; Staes et al., 2019). In support of this, one of the fixed mutations, P248Q, is not exclusively present in bonobos, but also found in chimpanzees, where it is polymorphic in nature. This polymorphism had already been documented and is linked to a reduction in anxiety and male impulsive aggression in chimpanzees (Staes et al., 2019). Similar to the previous study, the novel A-allele linked to this reduction in impulsive aggression was found at a much higher frequency in the chimpanzees sampled in this study, and it appears to have become fixed in bonobos. While the previous study included only 6 bonobos (Staes et al., 2019), our current study on a larger sample of 33 assumed unrelated bonobos confirms this result. The fixation of the allele linked to lower aggression and anxiety in bonobos, combined with the high number of bonobo-specific fixed amino acid changes in HTR1A are indicators that there has been selection for these behaviors in the ancestral *Pan* population.

Compared with bonobos, chimpanzees show 31% more polymorphic variation across all four genes, with 15 synonymous and 7 nonsynonymous SNVs present in chimpanzees versus 12 synonymous and three nonsynonymous SNVs in bonobos. It is important to note that 11 out of 23 SNVs in chimpanzees had very low MAFs ($\leq$5%), and were present in just one individual each in the sampled population. Although sequencing errors in the VCF data cannot be ruled out completely, the higher number of SNVs is in line with previous studies documenting greater haplotype diversity in chimpanzees, due to their larger estimated effective ancestral population size compared with bonobos (Prado-Martinez et al., 2014; de Manuel et al., 2016).

Some studies have reported higher behavioral similarity between western chimpanzees and bonobos, especially in patterns and levels of intersexual social bonding and proximity keeping (Boesch and Boesch-Acherman, 2000; Gomes and Boesch, 2009; Lehmann and Boesch, 2009). We therefore included a chimpanzee subspecies division of genetic variation in the appendix (SOM Table S2). Central chimpanzees showed a surprisingly low level of diversity in our candidate genes, with only three SNVs present, identical to the number found in western chimpanzees. Out of all four subspecies, central chimpanzees are expected to show the greatest haplotype and Y chromosome diversity and western chimpanzees the lowest (Prado-Martinez et al., 2014; de Manuel et al., 2016), but our sample size of the central chimpanzees was lower than for the other subspecies in some of the data sets, which could partly explain the lack of variance. It thus appears that the sequences of central and western chimpanzees show the least deviation from the bonobo sequences for these genes, but due to small sample sizes these results should not be overinterpreted. Recent studies have also documented ancient admixture between bonobos and chimpanzees, with an unexpected level of relatively recent gene flow, primarily seen between nonwestern chimpanzees (*P. t. troglodytes*, *P. t. elliotii*, *P. t. schweinfurthii*) and bonobos (de Manuel et al., 2016; Kuhlwilm et al., 2019). Based on this admixture, we would expect to see higher sequence similarity between bonobos and nonwestern chimpanzees but aside from low SNV variability in central chimpanzees, this was not the case for our four candidate genes. All the fixed substitutions and SNVs that we found were species-specific, meaning that there were no clear patterns of bonobo-specific variants matching variants of nonwestern chimpanzees more than the variants found in western chimpanzees, which would be expected in line with ancestral introgression theories (de Manuel et al., 2016; Kuhlwilm et al., 2019).

4.2. Behavioral function

Where either one or both *Pan* gene sequences differed from the human reference sequences, we investigated if polymorphic variation is present in humans at those same coordinates that have documented links with phenotypes to assess the potential behavioral impact of these sequence differences in *Pan*. For all four genes, we found that a majority of SNVs were human-specific, meaning that both *Pan* species had the same ancestral genotype. Many of these SNVs were outside of the coding region and linked to clinical phenotypes (schizophrenia, autism, substance addiction, and depression, see Table 4 for overview). Some variants like *OXTR* rs237887, rs237888, rs53576, rs237895, rs4564970, and *DRD2* rs4581480, were also linked to more relevant sociocognitive traits like empathy (Rodrigues et al., 2009; Wu et al., 2012), prosociality (Wilczyński et al., 2019), aggression (Johansson et al., 2012), maternal behavior (Riem et al., 2011; Toepfer et al., 2019), general sociality (Li et al., 2015; Poore and Waldman, 2020), and emotional processing (Peciña et al., 2013). It is possible that some of the variants might contribute to observed differences between humans and *Pan* in these respective traits. Other SNVs, like rs53576, have been included in ~200 scientific studies, with sometimes conflicting results. The interpretation of this SNV for its implication in an evolutionary context is therefore more difficult. The human-specific A-allele that is not found in *Pan*, has for example been associated with both higher (Laursen et al., 2014) and lower empathic capacity (Rodrigues et al., 2009). It is therefore difficult to conclude what the impact was of this variant on known human-*Pan* sociocognitive differences.

A small amount of SNVs showed allelic differences between the two *Pan* species, which is fascinating with regard to their behavioral dichotomy (MacLean, 2016). Especially for *OXTR*, the specific human behavioral associations of rs4686301(T) and rs237897(A), which are homologous in humans and bonobos but absent in chimpanzees, might be in line with known species differences in sociocognitive skills. It is important to note that the alleles related to better theory of mind, male prosociality and a stronger aversion for betrayal (Israel et al., 2009; Tabak et al., 2014; Wade et al., 2015) appear to have become fixed in bonobos, but are completely lacking in chimpanzees. Similarly, for *OXTR* rs2228485, the A allele linked to better reading of male facial expression in humans, became fixed in chimpanzees but no A allele is present in bonobos. While functionality of these alleles would need to be further investigated in *Pan* with functional assays, a potential explanation is that the ancestor of *Pan* was polymorphic at these positions, similar to humans, and that after the split of the two *Pan* species, different alleles were favored in each species. Cognitive tests indicate that bonobos are better at theory of mind and social causality (Herrmann et al., 2010) and make more eye contact than chimpanzees (Kano et al., 2015), but more tests are needed to quantify precise species differences in theory of mind (Krupenye and Call, 2019).

What is fascinating, is that the sex differences for prosociality and reading of facial expressions, are consistent with the species socioecology. Bonobo-specific *OXTR* rs237897(A) is primarily linked to increased male prosociality, while chimpanzee-specific *OXTR* rs2228485(A) is linked to better reading of male faces only. In bonobos, it has been theorized that males have evolved to be more prosocial through sexual selection (Hare et al., 2012; Hare, 2017). They will invest more in affiliative relationships with females than do chimpanzees, and behaviors like sexual coercion that occur frequently in chimpanzees, are rare in bonobos and typically met by female coalitionary defense (Tokuyama and Furuichi, 2016). *OXTR* rs237897(A) is thus a potential candidate that might have been the target of this selection process. As for *OXTR* rs2228485(A), the bias towards male faces might be in line with a selection for stronger male–male bonding in this species, thus favoring variants/skills that will facilitate these bonds. Male bonds are often highly affiliative and cooperative compared with male–female bonds, as shown for example in border patrols, hunting and mate guarding (Watts and Mitani, 2002; Muller and Mitani, 2005; Langergraber et al., 2009). Male bonobos on the other hand do not form coalitions with other males but rather rely on their mothers to maintain their position in the dominance hierarchy and have access to females for mating (Surbeck et al., 2011; Stevens et al., 2015). Selection for alleles favoring traits in one sex with no apparent negative effects for the opposite sex will ultimately lead to fixation of these alleles for the whole species.

Finally, in *DRD2*, two variants were identified with potential for sociocognitive difference between the two *Pan* species. For the first SNV, rs6277, the A allele that is linked to reduced impulse control (Della Torre et al., 2018) and reward-related memory (Richter et al., 2017) was only present in chimpanzees (MAF A = 0.040) and humans (MAF A = 0.244) but lacking in bonobos. As mentioned before, chimpanzees have been documented to show more impulsive behavior compared with bonobos, especially in the context of aggression (Wrangham, 2018), but also through increased risk-taking in feeding strategies (Rosati and Hare, 2012), and these effects might thus be mediated through differences in *DRD2* expression and/or affinity. Further systematic investigation within chimpanzees is needed to examine the effects of rs6277 allelic variants on receptor distribution, affinity, and behavior. In similar line, for rs11214613, the chimpanzee specific A allele present in all chimpanzees in our study is linked to an increased risk for impulsivity-related psychiatric disorders like substance addiction in humans (Wei et al., 2012).

5. Conclusions

Despite the high protein sequence stability in our candidate genes across ape species, a number of nonsynonymous variants were found that are polymorphic in nature within bonobos and chimpanzees, with genotype frequencies exceeding 5% in all genes but *OXTR* (Table 3). In chimpanzee *DRD2*, we also identified a polymorphic synonymous variant (rs6277) with promising links to behavioral phenotypes in humans. These SNVs offer valuable starting points for future behavior–genotype analyses to further explore the evolutionary past of the behavioral divergence in *Pan* and can be noninvasively genotyped at low cost. While much research has already been done on behavioral effects of *AVPR1A* promoter region variation in chimpanzees (for review, see, in press Hopkins and Latzman), studies could now also include M372T, the nonsynonymous SNV present at the C-terminal region of the chimpanzee AVPR1A receptor. Given the importance of the C-terminal region in signal transduction, mutations in this region could influence the functioning of the receptor (Ren et al., 2014). For dopamine, research in primates has mainly focused on receptor subtype D4 (Livak et al., 1995; Shimada et al., 2004; Garamszegi et al., 2014) and *DRD2* genotype–phenotype matching studies are lacking in *Pan*. The SNV causing the A76V substitution is present in the N-terminal dopamine-binding domain of the bonobo DRD2 receptor and offers potential for future study. Finally, while the literature on serotonin is currently skewed towards the serotonin transporter gene (reviewed in Staes et al., 2019), our study highlights potentially important bonobo-specific polymorphic variation in the gene coding for its receptor (*HTR1A*). Based on the results found for chimpanzees (Staes et al., 2019), we predict that the polymorphic variants present in the third intracellular loop of the receptor (T236P and T240P) offer great potential to explain within-species behavioral variation in aggression and anxiety in bonobos. Finally, for *OXTR* and *DRD2*, we also found interesting sequence differences that might contribute to known sociocognitive differences in humans, bonobos, and chimpanzees (rs4686301, rs237897, rs2228485, rs11214613). Given that all these variants became fixed in each species, further experimental assays testing their in vitro effects will be needed to confirm true functionality of the alleles that became fixed in *Pan*. To conclude, our results offer the first in-depth comparison of neurochemical receptor gene variation in *Pan* and put forward new variants for future behavior-genotype association studies in apes, which can increase our understanding of the evolution of social cognition in modern humans. The nature and strength of the genotype-phenotype associations in these closely related species should confirm to what extent the proximate neurochemical mechanisms regulating sociocognitive skills are uniquely human or shared with our close primate cousins.

Conflicts of interest

The authors declare that there are no conflicts of interest to report.

Acknowledgments

We thank all members of the Antwerp Primate Ethology and Evolution Lab at the University of Antwerp, the reviewers and the associate editor for helpful feedback on the project and manuscript. N.S. was funded by a postdoctoral fellowship awarded by the Research Foundation Flanders (FWO).

Appendix A. Supplementary Online Material

Supplementary Online Material to this article can be found online at https://doi.org/10.1016/j.jhevol.2021.102949.

References

Al-eitan, L.N., Jaradat, S.A., Hulse, G.K., Tay, G.K., 2012. Custom genotyping for substance addiction susceptibility genes in Jordanians of Arab descent. BMC Res. Notes 5, 497.
Apicella, C.L., Silk, J.B., 2019. The evolution of human cooperation. Curr. Biol. 29, R447–R450.
Arnold, C., Matthews, L.J., Nunn, C.L., 2010. The 10kTrees website: A new online resource for primate phylogeny. Evol. Anthropol. 19, 114–118.
Babb, P.L., Fernandez-Duque, E., Schurr, T.G., 2010. *AVPR1A* sequence variation in monogamous owl monkeys (Aotus azarai) and its implications for the evolution of Platyrrhine social behavior. J. Mol. Evol. 71, 279–297.
Babb, P.L., Fernandez-Duque, E., Schurr, T.G., 2015. Oxytocin receptor gene sequences in owl monkeys and other primates show remarkable interspecific regulatory and protein coding variation. Mol. Phylogenet. Evol. 91, 160–177.
Barr, C.S., Newman, T.K., Lindell, S., Shannon, C., Champoux, M., Lesch, K.P., Suomi, S.J., Goldman, D., Higley, J.D., 2004. Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. Arch. Gen. Psychiatr. 61, 1146–1152.
Bawor, M., Dennis, B.B., Tan, C., Pare, G., Varenbut, M., Daiter, J., Plater, C., Worster, A., Marsh, D.C., Steiner, M., Anglin, R., Desai, D., 2015. Contribution of *BDNF* and *DRD2* genetic polymorphisms to continued opioid use in patients receiving methadone treatment for opioid use disorder: an observational study. Addiction Sci. Clin. Pract. 10, 19.
Bernhard, R., Chaponis, J., Siburian, R., Gallagher, P., Ransohoff, K., Wikler, D., Perlis, R., Greene, J., 2016. Variation in the oxytocin receptor gene (*OXTR*) is associated with differences in moral judgment. Soc. Cognit. Affect Neurosci. 11, 1872–1881.
Besenbacher, S., Hvilsom, C., Marques-Bonet, T., Mailund, T., Schierup, M.H., 2019. Direct estimation of mutations in great apes reconciles phylogenetic dating. Nat. Ecol. Evolut. 3, 286–292.
Boender, A.J., Young, L.J., 2020. Oxytocin, vasopressin and social behavior in the age of genome editing: A comparative perspective. Horm. Behav. 124, 104780.
Boesch, C., 2007. What makes us human (*Homo sapiens*)? The challenge of cognitive cross-species comparison. J. Comp. Psychol. 121, 227–240.
Boesch, C., Boesch-Acherman, H., 2000. The Chimpanzees of the Tai Forest: Behavioural Ecology and Evolution. Cambridge University Press, Cambridge.
Call, J., Tomasello, M., 2008. Does the chimpanzee have a theory of mind? 30 years later. Trends Cognit. Sci. 12, 187–192.
Castellano, D., Munch, K., 2020. Population genomics in the great apes. In: Dutheil, J.Y. (Ed.), Statistical Population Genomics. Humana Press, New York, pp. 453–463.
Celorrio, D., Muñoz, X., Amiano, P., Dorronsoro, M., Bujanda, L., Sánchez, M., Molina-montes, E., Navarro, C., Chirlaque, M.D., Maríahuerta, J., Ardanaz, E., Barricarte, A., Rodriguez, L., Duell, E.J., Hijona, E., Herreros-villanueva, M., Sala, N., Alfonso-sánchez, M.A., de Pancorbo, M.M., 2016. Influence of dopaminergic system genetic variation and lifestyle factors on excessive alcohol consumption. Alcohol Alcohol. 51, 258–267.
Chang-Chih, Tsou, Chou, H.-W., Ho, P.-S., Kuo, S.-C., Chen, C.-Y., Huang, C.-C., Liang, C.-S., Lu, R.-B., Huang, S.-Y., 2019. *DRD2* and *ANKK1* genes associate with late-onset heroin dependence in men. World J. Biol. Psychiatr. 20, 605–615.
Choi, Y., Chan, A., 2015. PROVEAN web server: a tool to predict the functional effect of amino acid substitutions and indels. Bioinformatics 31, 2745–2747.

Court, M.H., 2008. A simple calculator to determine whether observed genotype frequencies are consistent with Hardy-Weinberg equilibrium. http://www.tufts.edu/~mcourt01/Documents/Court lab - HW calculator.xls.
Cronin, K.A., De Groot, E., Stevens, J.M.G., 2015. Bonobos show limited social tolerance in a group setting: A comparison with chimpanzees and a test of the relational model. Folia Primatol. 86, 164–177.
de Manuel, M., Kuhlwilm, M., Frandsen, P., Sousa, V.C., Desai, T., Prado-Martinez, J., Hernandez-Rodriguez, J., Dupanloup, I., Lao, O., Hallast, P., Schmidt, J.M., Heredia-Genestar, J.M., Benazzo, A., Barbujani, G., Peter, B.M., Kuderna, L.F.K., Casals, F., Angedakin, S., Arandjelovic, M., Boesch, C., Kühl, H., Vigilant, L., Langergraber, K., Novembre, J., Gut, M., Gut, I., Navarro, A., Carlsen, F., Andrés, A.M., Siegismund, H.R., Scally, A., Excoffier, L., Tyler-Smith, C., Castellano, S., Xue, Y., Hvilsom, C., Marques-Bonet, T., 2016. Chimpanzee genomic diversity reveals ancient admixture with bonobos. Science 354, 477–481.
De Waal, F.B., Boesch, C., Horner, V., Whiten, A., 2008. Comparing social skills of children and apes. Science 319, 569.
Della Torre, O.H., Paes, L.A., Henriques, T.B., Mello, M.P. de, Celeri, E.H.R.V., Dalgalarrondo, P., Guerra-Júnior, G., Dos Santos-Júnior, A., 2018. Dopamine D2 receptor gene polymorphisms and externalizing behaviors in children and adolescents. BMC Med. Genet. 19, 65.
Duan, Z., He, M., Zhang, J., Chen, K., Li, B., Wang, J., 2015. Assessment of functional tag single nucleotide polymorphisms within the *DRD2* gene as risk factors for post-traumatic stress disorder in the Han Chinese population. J. Affect. Disord. 188, 210–217.
Ebstein, R.P., Israel, S., Chew, S.H., Zhong, S., Knafo, A., 2010. Genetics of human social behavior. Neuron 65, 831–844.
Eriksson, J., Hohmann, G., Boesch, C., Vigilant, L., 2004. Rivers influence the population genetic structure of bonobos (*Pan paniscus*). Mol. Ecol. 13, 3425–3435.
Fink, S., Excoffier, L., Heckel, G., 2007. High variability and non-neutral evolution of the mammalian *avpr1a* gene. BMC Evol. Biol. 7, 176.
Furuichi, T., 2011. Female contributions to the peaceful nature of bonobo society. Evol. Anthropol. 20, 131–142.
Garamszegi, L.Z., Mueller, J.C., Markó, G., Szász, E., Zsebok, S., Herczeg, G., Eens, M., Török, J., 2014. The relationship between *DRD4* polymorphisms and phenotypic correlations of behaviors in the collared flycatcher. Ecol. Evolut. 4, 1466–1479.
Gomes, C.M., Boesch, C., 2009. Wild chimpanzees exchange meat for sex on a long-term basis. PLoS One 4, e5116.
Graffelman, J., 2015. Exploring diallelic genetic markers: The HardyWeinberg package. J. Stat. Software 64, 1–23.
Guan, F., Lin, H., Chen, G., Li, L., Chen, T., Liu, X., Han, J., Li, T., 2016. Evaluation of association of common variants in *HTR1A* and *HTR5A* with schizophrenia and executive function. Sci. Rep. 6, 38048.
Hale, M.L., Burg, T.M., Steeves, T.E., 2012. Sampling for microsatellite-based population genetic studies: 25 to 30 individuals per population is enough to accurately estimate allele frequencies. PLoS One 7, e45170.
Hamidovic, A., Dlugos, A., Skol, A., Palmer, A.A., Wit, H. De, 2010. Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: An exploratory study with d-Amphetamine in healthy participants. Exp. Clin. Psychopharmacol. 17, 374–383.
Hammock, E.A.D., Young, L.J., 2005. Microsatellite instability generates diversity in brain and sociobehavioral traits. Science 308, 1630–1634.
Hare, B., 2017. Survival of the friendliest: Homo sapiens evolved via selection for prosociality. Annu. Rev. Psychol. 68, 155–186.
Hare, B., Kwetuenda, S., 2010. Bonobos voluntarily share their own food with others. Curr. Biol. 20, 230–231.
Hare, B., Melis, A.P., Woods, V., Hastings, S., Wrangham, R., 2007. Tolerance allows bonobos to outperform chimpanzees on a cooperative task. Curr. Biol. 17, 619–623.
Hare, B., Wobber, V., Wrangham, R., 2012. The self-domestication hypothesis: Evolution of bonobo psychology is due to selection against aggression. Anim. Behav. 83, 573–585.
He, M., He, H., Yang, L., Zhang, J., Chen, K., Duan, Z., 2019. Functional tag SNPs inside the *DRD2* gene as a genetic risk factor for major depressive disorder in the Chinese Han population. Int. J. Clin. Exp. Pathol. 12, 628–639.
Hecht, M., Bromberg, Y., Rost, B., 2015. Better prediction of functional effects for sequence variants From VarI-SIG 2014: Identification and annotation of genetic variants in the context of structure, function and disease. BMC Genom. 16, S1.
Herrmann, E., Call, J., Hernandez-Lloreda, M.V., Hare, B., Tomasello, M., 2007. Humans have evolved specialised skills of social cognition: The cultural intelligence hypothesis. Science 317, 1360–1366.
Herrmann, E., Hare, B., Call, J., Tomasello, M., 2010. Differences in the cognitive skills of bonobos and chimpanzees. PLoS One 5, e12438.
Hirvonen, M.M., Lumme, V., Hirvonen, J., Pesonen, U., Någren, K., Vahlberg, T., Scheinin, H., Hietala, J., 2009. C957T polymorphism of the human dopamine D2 receptor gene predicts extrastriatal dopamine receptor availability in vivo. Progress in Neuropsychopharmacol. Biol. Psychiatr. 33, 630–636.
Hopkins, W.D., Donaldson, Z.R., Young, L.J., 2012. A polymorphic indel containing the RS3 microsatellite in the 5' flanking region of the vasopressin V1a receptor gene is associated with chimpanzee (Pan troglodytes) personality. Gene Brain Behav. 11, 552–558.
Hopkins, W.D., Latzman, R.D., in press. Role of oxytocin and vasopressin V1a receptor variation on personality , social behavior, social cognition, and the brain in nonhuman primates with a specific emphasis in chimpanzee. In: Wilczynski, W., Brosnan, S.F. (Eds.), Social Cooperation and Conflict: Biological Mechanisms at the Interface. Cambridge University Press, Cambridge.
Hopkins, W.D., Lyn, H., Cantalupo, C., 2009. Volumetric and lateralized differences in selected brain regions of chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). Am. J. Primatol. 71, 988–997.
Hopkins, W.D., Stimpson, C.D., Sherwood, C.C., 2017. Social cognition and brain organization in chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). In: Hare, B., Yamamoto, S. (Eds.), Bonobos: Unique in Mind, Brain and Behavior. Oxford University Press, Oxford, pp. 199–213.
Huerta-Cepas, J., Serra, F., Bork, P., 2016. ETE 3: Reconstruction, analysis, and visualization of phylogenomic data. Mol. Biol. Evol. 33, 1635–1638.
Idani, G., 1990. Relations between unit-groups of bonobos at Wamba, Zaire: Encounters and temporary fusions. Afr. Stud. Monogr. 11, 153–186.
Inoue-murayama, M., Yokoyama, C., Yamanashi, Y., Weiss, A., 2018. Common marmoset (*Callithrix jacchus*) personality, subjective well-being, hair cortisol level genotypes. Sci. Rep. 8, 10255.
Insel, T.R., 2010. The challenge of translation in social neuroscience: A review of oxytocin, vasopressin, and affiliative behavior. Neuron 65, 768–779.
Israel, S., Lerer, E., Shalev, I., Uzefovsky, F., Riebold, M., Laiba, E., Bachner-Melman, R., Maril, A., Bornstein, G., Knafo, A., Ebstein, R.P., 2009. The oxytocin receptor (OXTR) contributes to prosocial fund allocations in the Dictator Game and the social value orientations task. PLoS One 4, e5535.
Issa, H.A., Staes, N., Diggs-Galligan, S., Stimpson, C.D., Gendron-Fitzpatrick, A., Taglialatela, J.P., Hof, P.R., Hopkins, W.D., Sherwood, C.C., 2019. Comparison of bonobo and chimpanzee brain microstructure reveals differences in socio-emotional circuits. Brain Struct. Funct. 224, 239–251.
Johansson, A., Bergman, H., Corander, J., Waldman, I.D., Karrani, N., Salo, B., Jern, P., Algars, M., Sandnabba, K., Santtila, P., Westberg, L., 2012. Alcohol and aggressive behavior in men-moderating effects of oxytocin receptor gene (OXTR) polymorphisms. Gene Brain Behav. 11, 214, 212.
Julian, M., King, A., Bocknek, E., Mantha, B., Beeghly, M., Rosenblum, K., Muzik, M., 2019. Associations between oxytocin receptor gene (*OXTR*) polymorphisms, childhood trauma, and parenting behavior. Dev. Psychol. 10, 2135–2146.
Jurek, B., Neumann, I.D., 2018. The oxytocin receptor: From intracellular signaling to behavior. Physiol. Rev. 98, 1805–1908.
Kanders, S.H., Pisanu, C., Bandstein, M., Jonsson, J., Castelao, E., Pistis, G., Gholam-Rezaee, M., Eap, C.B., Preisig, M., Schiöth, H.B., Mwinyi, J., 2020. A pharmacogenetic risk score for the evaluation of major depression severity under treatment with antidepressants. Drug Dev. Res. 81, 102–113.
Kano, F., Call, J., 2014. Cross-species variation in gaze following and conspecific preference among great apes, human infants and adults. Anim. Behav. 91, 136–149.
Kano, F., Hirata, S., Call, J., 2015. Social attention in the two species of pan: Bonobos make more eye contact than chimpanzees. PLoS One 10, 1–14.
Kent, W., 2002. BLAT - the BLAST-like alignment tool. Genome Res. 12, 656–664.
King, L.B., Walum, H., Inoue, K., Eyrich, N.W., Young, L.J., 2016. Variation in the oxytocin receptor gene predicts brain region – specific expression and social attachment. Biol. Psychiatr. 80, 160–169.
Knafo, A., Israel, S., Darvasi, A., Bachner-Melman, R., Uzefovsky, F., Cohen, L., Feldman, E., Lerer, E., Laiba, E., Raz, Y., Nemanov, L., Gritsenko, I., Dina, C., Agam, G., Dean, B., Bornstein, G., Ebstein, R.P., 2008. Individual differences in allocation of funds in the dictator game associated with length of the arginine vasopressin 1a receptor RS3 promoter region and correlation between RS3 length and hippocampal mRNA. Gene Brain Behav. 7, 266–275.
Kranz, T.M., Kopp, M., Waltes, R., Sachse, M., Duketis, E., Jarczok, T., Degenhardt, F., Görgen, K., Meyer, J., Freitag, C., Chiocchetti, A., 2016. Meta-analysis and association of two common polymorphisms of the human oxytocin receptor gene in autism spectrum disorder. Autism Res. 9, 1036–1045.
Kristiaensen, K., 2004. Molecular mechanisms of ligand binding, signaling, and regulation within the superfamily of G-protein-coupled receptors: molecular modeling and mutagenesis approaches to receptor structure and function. Pharmacol. Therapeut. 103, 21–80.
Krupenye, C., Call, J., 2019. Theory of mind in animals: Current and future directions. Wiley Interdiscipl. Rev. Cognit. Sci. 10, e1503.
Kuhlwilm, M., Han, S., Sousa, V.C., Excoffier, L., Marques-bonet, T., 2019. Ancient admixture from an extinct ape lineage into bonobos. Nat. Ecol. Evolut. 3, 957–965.
Kumar, S., Stecher, G., Suleski, M., Hedges, S.B., 2017. TimeTree: a resource for timelines, timetrees, and divergence times. Mol. Biol. Evol. 34, 1812–1819.
Langergraber, K., Mitani, J., Vigilant, L., 2009. Kinship and social bonds in female chimpanzees (*Pan troglodytes*). Am. J. Primatol. 71, 840–851.
Laursen, H.R., Siebner, H.R., Haren, T., Madsen, K., Grønlund, R., Hulme, O., Henningsson, S., 2014. Variation in the oxytocin receptor gene is associated with behavioral and neural correlates of empathic accuracy. Front. Behav. Neurosci. 8, 423.
Leavens, D.A., Bard, K.A., Hopkins, W.D., 2019. The mismeasure of ape social cognition. Anim. Cognit. 22, 487–504.
Lehmann, J., Boesch, C., 2009. Sociality of the dispersing sex: the nature of social bonds in West African female chimpanzees, *Pan troglodytes*. Anim. Behav. 77, 377–387.
Lerer, E., Levi, S., Salomon, S., Darvasi, a, Yirmiya, N., Ebstein, R.P., 2008. Association between the oxytocin receptor (*OXTR*) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. Mol. Psychiatr. 13, 980–988.

Li, J., Zhao, Y., Li, R., Broster, L.S., Zhou, C., Yang, S., 2015. Association of oxytocin receptor gene (*OXTR*) rs53576 polymorphism with sociality: A meta-analysis. PLoS One 10, 1–16.

Liu, Q., Xu, Y., Mao, Y., Ma, Y., Wang, M., Han, H., Cui, W., Yuan, W., Payne, T.J., Xu, Y., Li, M.D., Yang, Z., 2020. Genetic and epigenetic analysis revealing variants in the NCAM1–TTC12–ANKK1–DRD2 cluster associated significantly with nicotine dependence in Chinese Han smokers. Nicotine Tob. Res. 22, 1301–1309.

Livak, K.J., Rogers, J., Lichter, J.B., 1995. Variability of dopamine D4 receptor (*DRD4*) gene sequence within and among nonhuman primate species. Proc. Natl. Acad. Sci. USA 92, 427–431.

LoParo, D., Waldman, I., 2015. The oxytocin receptor gene (*OXTR*) is associated with autism spectrum disorder: a meta-analysis. Mol. Psychiatr. 20, 640–646.

Loughlin, J.O., Sylvestre, M., Low, N.C., Engert, J.C., 2014. Genetic variants and early cigarette smoking and nicotine dependence phenotypes in adolescents. PLoS One 9, e115716.

Lucht, M.J., Barnow, S., Sonnenfeld, C., Rosenberger, A., Grabe, H.J., Schroeder, W., Völzke, H., Freyberger, H.J., Herrmann, F.H., Kroemer, H., Rosskopf, D., 2009. Associations between the oxytocin receptor gene (*OXTR*) and affect, loneliness and intelligence in normal subjects. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 33, 860–866.

Lucht, M.J., Barnow, S., Sonnenfeld, C., Ulrich, I., Grabe, J.H., Schroeder, W., Völzke, H., Freyberger, H.J., John, U., Herrmann, F.H., Kroemer, H., Rosskopf, D., 2013. Associations between the oxytocin receptor gene (*OXTR*) and "mind-reading" in humans—An exploratory study. Nord. J. Psychiatr. 67, 15–21.

MacLean, E.L., 2016. Unraveling the evolution of uniquely human cognition. Proc. Natl. Acad. Sci. USA 113, 6348–6354.

Malik, A., Zai, C., Abu, Z., Nowrouzi, B., Beitchman, J., 2012. The role of oxytocin and oxytocin receptor gene variants in childhood-onset aggression. Gene Brain Behav. 11, 545–551.

Masson, J., Emerit, M.B., Hamon, M., Darmon, M., 2012. Serotonergic signaling: Multiple effectors and pleiotropic effects. Wiley Interdiscipl. Rev.: Membrane Transport and Signaling 1, 685–713.

Mattson, R., Cameron, N., Middleton, F., Starr, L., Davila, J., Johnson, M., 2019. Oxytocin receptor gene (*OXTR*) links to marital quality via social support behavior and perceived partner responsiveness. J. Fam. Psychol. 33, 44–53.

Mekli, K., Payton, A., Miyajima, F., Platt, H., Thomas, E., Downey, D., Lloyd-Williams, K., Chase, D., Toth, Z.G., Elliott, R., Ollier, W.E., Anderson, I.M., Deakin, J.F.W., Bagdy, G., Juhasz, G., 2011. The *HTR1A* and *HTR1B* receptor genes influence stress-related information processing. Eur. Neuropsychopharmacol. 21, 129–139.

Moore, J., 1996. Savanna chimpanzees, referential models and the last common ancestor. In: Mcgrew, W.C., Marchant, L.F., Nishida, T. (Eds.), Great Ape Societies. Cambridge University Press, Cambridge, pp. 275–292.

Muller, M.M., Mitani, J.C., 2005. Conflict and cooperation in wild chimpanzees. Adv. Stud. Behav. 35, 275–331.

Myers, A., Williams, L., Gatt, J., McAuley-Clark, E., Dobson-Stone, C., Schofield, P., Nemeroff, C., 2014. Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress. J. Psychiatr. Res. 59, 93–100.

Nair, H.P., Young, L.J., 2006. Vasopressin and pair-bond formation: genes to brain to behavior. Physiology 21, 146–152.

Nkam, I., Ramoz, N., Breton, F., Mallet, J., Gorwood, P., Dubertret, C., 2017. Impact of *DRD2/ANKK1* and *COMT* polymorphisms on attention and cognitive functions in schizophrenia. PLoS One 12, e0170147.

Nyman, E.S., Sulkava, S., Soronen, P., Miettunen, J., Joukamaa, M., Ma, P., 2011. Interaction of early environment , gender and genes of monoamine neurotransmission in the aetiology of depression in a large population-based Finnish birth cohort. Br. Med. J. Open 1, e000087.

Okhovat, M., Berrio, A., Wallace, G., Ophir, A.G., Phelps, S.M., 2015. Sexual fidelity trade-offs promote regulatory variation in the prairie vole brain. Science 350, 1371–1374.

Omasits, U., Ahrens, C.H., Müller, S., Wollscheid, B., 2014. Protter: Interactive protein feature visualization and integration with experimental proteomic data. Bioinformatics 30, 884–886.

Peciña, M., Mickey, B.J., Love, T., Wang, H., Langenecker, S.A., Hodgkinson, C., Shen, P., Villafuerte, S., Hsu, D., Sara, L., Stohler, C.S., Goldman, D., Zubieta, J., 2013. *DRD2* polymorphisms modulate reward and emotion processing, dopamine neurotransmission and openness to experience. Cortex 49, 877–890.

Poore, H., Waldman, I., 2020. The association of oxytocin receptor gene (*OXTR*) polymorphisms with antisocial behavior: A meta-analysis. Behav. Genet. 50, 161–173.

Prado-Martinez, J., Sudmant, P.H., Kidd, J.M., Li, H., Kelley, J.L., Lorente-Galdos, B., Veeramah, K.R., Woerner, A.E., O'Connor, T.D., Santpere, G., Cagan, A., Theunert, C., Casals, F., Laayouni, H., Munch, K., Hobolth, A., Halager, A.E., Malig, M., Hernandez-Rodriguez, J., Hernando-Herraez, I., Prüfer, K., Pybus, M., Johnstone, L., Lachmann, M., Alkan, C., Twigg, D., Petit, N., Baker, C., Hormozdiari, F., Fernandez-Callejo, M., Dabad, M., Wilson, M.L., Stevison, L., Camprubí, C., Carvalho, T., Ruiz-Herrera, A., Vives, L., Mele, M., Abello, T., Kondova, I., Bontrop, R.E., Pusey, A., Lankester, F., Kiyang, J.A., Bergl, R.A., Lonsdorf, E., Myers, S., Ventura, M., Gagneux, P., Comas, D., Siegismund, H., Blanc, J., Agueda-Calpena, L., Gut, M., Fulton, L., Tishkoff, S.A., Mullikin, J.C., Wilson, R.K., Gut, I.G., Gonder, M.K., Ryder, O.A., Hahn, B.H., Navarro, A., Akey, J.M., Bertranpetit, J., Reich, D., Mailund, T., Schierup, M.H., Hvilsom, C., Andrés, A.M., Wall, J.D., Bustamante, C.D., Hammer, M.F., Eichler, E.E., Marquès-Bonet, T., 2014. Great ape genetic diversity and population history. Nature 499, 471–475.

R Core Team, 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna.

Reinartz, G.E., Karron, J.D., Phillips, R.B., Weber, J.L., 2000. Patterns of microsatellite polymorphism in the range-restricted bonobo (*Pan paniscus*): Considerations for interspecific comparison with chimpanzees (*P. troglodytes*). Mol. Ecol. 9, 315–328.

Reis, M. dos, Gunnell, G.F., Barba-Montoya, J., Wilkins, A., Yang, Z., Yoder, A.D., 2018. Using phylogenomic data to explore the effects of relaxed clocks and calibration strategies on divergence time estimation: primates as a test case. Syst. Biol. 67, 594–615.

Ren, D., Chin, K.R., French, J.A., 2014. Molecular variation in *AVP* and *AVPR1a* in New World monkeys (Primates , Platyrrhini): Evolution and implications for social monogamy. PLoS One 9, e111638.

Richter, A., Barman, A., Wüstenberg, T., Soch, J., Schanze, D., Deibele, A., Behnisch, G., Assmann, A., Klein, M., Zenker, M., Seidenbecher, C., Schott, B.H., 2017. Neural manifestations of reward memory in carriers of low-expressing versus high-expressing genetic variants of the dopamine D2 receptor. Front. Psychol. 8, 654.

Riem, M.M.E., Pieper, S., Out, D., Bakermans-Kranenburg, M.J., van IJzendoorn, M.H., 2011. Oxytocin receptor gene and depressive symptoms associated with physiological reactivity to infant crying. Soc. Cognit. Affect Neurosci. 6, 294–300.

Rilling, J.K., Scholz, J., Preuss, T.M., Glasser, M.F., Errangi, B.K., Behrens, T.E., 2012. Differences between chimpanzees and bonobos in neural systems supporting social cognition. Soc. Cognit. Affect Neurosci. 7, 369–379.

Rodrigues, S.M., Saslow, L.R., Garcia, N., John, O.P., Keltner, D., 2009. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. Proc. Natl. Acad. Sci. USA 106, 21437–21441.

Rogers, C.N., Ross, A.P., Sahu, S.P., Siegel, E.R., Jeromy, M., Cree, M.A., Stopa, E.G., Young, L.J., James, K., 2018. Oxytocin- and arginine vasopressin-containing fibers in the cortex of humans, chimpanzees, and rhesus macaques. Am. J. Primatol. 80, e22875.

Rosati, A.G., Hare, B., 2012. Decision making across social contexts: Competition increases preferences for risk in chimpanzees and bonobos. Anim. Behav. 84, 869e879.

Sakurai, H., Bies, R.R., Stroup, S.T., Keefe, R.S.E., Rajji, T.K., Suzuki, T., Mamo, D.C., Pollock, B.G., Watanabe, K., Mimura, M., Uchida, H., 2012. Dopamine D2 receptor occupancy and cognition in schizophrenia: Analysis of the CATIE data. Schizophr. Bull. 39, 564–574.

Savelieva, K., Hintsanen, M., Dobewall, H., Jokela, M., Pulkki-Råback, L., Elovainio, M., Seppälä, I., Lehtimäki, T., Raitakari, O., Keltikangas-Järvinen, L., 2019. The role of oxytocinergic genes in the intergenerational transmission of parent-child relationship qualities. Horm. Behav. 114, 104540.

Scally, A., Dutheil, J.Y., Hillier, L.W., Jordan, G.E., Goodhead, I., Herrero, J., Hobolth, A., Lappalainen, T., Mailund, T., Marques-bonet, T., Mccarthy, S., Montgomery, S.H., Schwalie, P.C., Tang, Y.A., Ward, M.C., Xue, Y., Yngvadottir, B., Alkan, C., Andersen, L.N., Ayub, Q., Ball, E.V., Beal, K., Bradley, B.J., Chen, Y., Clee, C.M., Fitzgerald, S., Graves, T.A., Gu, Y., Heath, P., Heger, A., Karakoc, E., Kolb-kokocinski, A., Laird, G.K., Lunter, G., Meader, S., Mort, M., Mullikin, J.C., Munch, K., Connor, T.D.O., Simpson, J.T., Stenson, P.D., Turner, D.J., Vigilant, L., Vilella, A.J., Whitener, W., Zhu, B., Mundy, N.I., Ning, Z., Odom, D.T., Ponting, C.P., Quail, M.A., Ryder, O.A., Searle, S.M., Warren, W.C., Wilson, R.K., Schierup, M.H., Rogers, J., Tyler-smith, C., Durbin, R., 2012. Insights into hominid evolution from the gorilla genome sequence. Nature 483, 169–175.

Sherry, S., Ward, M., Kholodov, M., Baker, J., Phan, L., Smigielski, E., Sirotkin, K., 2001. dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 29, 308–311.

Shimada, M.K., Inoue-Murayama, M., Ueda, Y., Maejima, M., Murayama, Y., Takenaka, O., Hayasaka, I., Ito, S., 2004. Polymorphism in the second intron of dopamine receptor D4 gene in humans and apes. Biochem. Biophys. Res. Commun. 316, 1186–1190.

Sipilä, T., Kananen, L., Greco, D., Donner, J., Silander, K., Terwilliger, J.D., Auvinen, P., Peltonen, L., Lönnqvist, J., Pirkola, S., Partonen, T., Hovatta, I., 2010. An association analysis of circadian genes in anxiety disorders. Biol. Psychiatr. 67, 1163–1170.

Skuse, D.H., Gallagher, L., 2011. Genetic influences on social cognition. Pediatr. Res. 69, 85–91.

Skuse, D.H., Lori, A., Cubells, J.F., Lee, I., Conneely, K.N., Puura, K., Lehtimäki, T., Binder, E.B., Young, L.J., 2014. Common polymorphism in the oxytocin receptor gene (OXTR) is associated with human social recognition skills. Proc. Natl. Acad. Sci. USA 111, 1987–1992.

Spielmann, M., Mundlos, S., 2016. Looking beyond the genes: The role of non-coding variants in human disease. Hum. Mol. Genet. 25, R157–R165.

Staes, N., Koski, S.E., Helsen, P., Fransen, E., Eens, M., Stevens, J.M.G., 2015. Chimpanzee sociability is associated with vasopressin (*Avpr1a*) but not oxytocin receptor gene (*OXTR*) variation. Horm. Behav. 75, 84–90.

Staes, N., Sherwood, C.C., Freeman, H., Brosnan, S.F., Shapiro, S.J., Hopkins, W.D., Bradley, B.J., 2019. Serotonin receptor 1A variation is associated with anxiety and agonistic behavior in chimpanzees. Mol. Biol. Evol. 36, 1418–1429.

Staes, N., Smaers, J.B., Kunkle, A.E., Hopkins, W.D., Bradley, B.J., Sherwood, C.C., 2018. Evolutionary divergence of neuroanatomical organization and related genes in chimpanzees and bonobos. Cortex 118, 154–164.

Staes, N., Weiss, A., Helsen, P., Korody, M., Eens, M., Stevens, J.M.G., 2016. Bonobo personality traits are heritable and associated with vasopressin receptor gene 1a variation. Sci. Rep. 6, 38193.

Stevens, J.M.G., de Groot, E., Staes, N., 2015. Relationship quality in captive bonobo groups. Behaviour 152, 259–283.

Surbeck, M., Mundry, R., Hohmann, G., 2011. Mothers matter! Maternal support, dominance status and mating success in male bonobos (*Pan paniscus*). Proc. R. Soc. B 278, 590–598.

Tabak, B., McCullough, M., Carver, C., Pedersen, E., Cuccaro, M., 2014. Variation in oxytocin receptor gene (*OXTR*) polymorphisms is associated with emotional and behavioral reactions to betrayal. Soc. Cognit. Affect Neurosci. 9, 810–816.

Tan, J., Hare, B., 2013. Bonobos share with strangers. PLoS One 8, e51922.

Teixeira, C., Filippo, C. De, Weihmann, A., Meneu, J.R., Racimo, F., Dannemann, M., Nickel, B., Fischer, A., Halbwax, M., Andre, C., Atencia, R., Andr, A.M., Meyer, M., Svante, P., 2015. Long-term balancing selection in *LAD1* maintains a missense trans-species polymorphism in humans, chimpanzees, and bonobos. Mol. Biol. Evol. 32, 1186–1196.

The 1000 genomes project consortium, 2015. A global reference for human genetic variation. Nature 526, 68–74.

Toepfer, P., O'Donnell, K., Entringer, S., Heim, C., Lin, D., MacIsaac, J., Kobor, M., Meaney, M., Provençal, N., Binder, E., Wadhwa, P., Buss, C., 2019. A role of oxytocin receptor gene brain tissue expression quantitative trait locus rs237895 in the intergenerational transmission of the effects of maternal childhood maltreatment. J. Am. Acad. Child Adolesc. Psychiatry 58, 1207–1216.

Tokuyama, N., Furuichi, T., 2016. Do friends help each other? Patterns of female coalition formation in wild bonobos at Wamba. Anim. Behav. 119, 27–35.

Tomasello, M., Carpenter, M., Call, J., Behne, T., Moll, H., 2005. Understanding and sharing intentions: The origins of cultural cognition. Behav. Brain Sci. 28, 675–691.

Tomasello, M., Herrmann, E., 2010. Ape and human cognition: What's the difference? Curr. Dir. Psychol. Sci. 19, 3–8.

Turner, J.H., Gelasco, A.K., Raymond, J.R., 2004. Calmodulin interacts with the third intracellular loop of the serotonin 5-hydroxytryptamine 1A receptor at two distinct sites: Putative role in receptor phosphorylation by protein kinase C. J. Biol. Chem. 279, 17027–17037.

Van Coillie, S., Galbusera, P., Roeder, A.D., Schempp, W., Stevens, J.M.G., Leus, K., Reinartz, G., Pereboom, Z., 2008. Molecular paternity determination in captive bonobos and the impact of inbreeding on infant mortality. Anim. Conserv. 11, 306–312.

Voisey, J., Swagell, C., Hughes, I., Lawford, B., Young, R., Morris, C., 2012. A novel *DRD2* single-nucleotide polymorphism associated with schizophrenia predicts age of onset: HapMap tag-single-nucleotide polymorphism analysis. Genet. Test. Mol. Biomarkers 16, 77–81.

Wade, M., Hoffmann, T.J., Jenkins, J.M., 2015. Gene–environment interaction between the oxytocin receptor (*OXTR*) gene and parenting behaviour on children's theory of mind. Soc. Cognit. Affect Neurosci. 10, 1749–1758.

Walter, H., 2012. Social cognitive neuroscience of empathy: Concepts, circuits, and genes. Emot. Rev. 4, 9–17.

Watts, D.P., Mitani, J.C., 2002. Hunting behavior of chimpanzees at Ngogo, Kibale National Park, Uganda. Int. J. Primatol. 23, 1–28.

Wei, J., Chu, C., Wang, Y., Yang, Y., Wang, Q., Li, T., Zhang, L., Ma, X., 2012. Association study of 45 candidate genes in nicotine dependence in Han Chinese. Addict. Behav. 37, 622–626.

Wilczyński, K., Siwiec, A., Janas-Kozik, M., 2019. Systematic review of literature on single-nucleotide polymorphisms within the oxytocin and vasopressin receptor genes in the development of social cognition dysfunctions in individuals suffering from autism spectrum disorder. Front. Psychiatr. 10, 380.

Wrangham, R.W., 2018. Two types of aggression in human evolution. Proc. Natl. Acad. Sci. USA 115, 245e253.

Wu, N., Li, Z., Su, Y., 2012. The association between oxytocin receptor gene polymorphism (*OXTR*) and trait empathy. J. Affect. Disord. 138, 468–472.

Wu, S., Jia, M., Ruan, Y., Liu, J., Guo, Y., Shuang, M., Gong, X., Zhang, Y., Yang, X., Zhang, D., 2005. Positive association of the oxytocin receptor gene (*OXTR*) with autism in the Chinese Han population. Biol. Psychiatr. 58, 74–77.

Xiaoxi, L., Yoshiya, K., Takafumi, S., Takeshi, O., Shinko, K., Toshiro, S., Hisami, N., Ohiko, H., Ryoichi, N., Mamoru, T., Tadashi, U., Yukiko, K., Taku, M., Nobumasa, K., Katsushi, T., Tsukasa, S., 2010. Association of the oxytocin receptor (*OXTR*) gene polymorphisms with autism spectrum disorder (ASD) in the Japanese population. J. Hum. Genet. 55, 137–141.

Yamamoto, S., 2015. Non-reciprocal but peaceful fruit sharing in wild bonobos in Wamba. Behaviour 152, 335–357.

Yamamoto, S., Furuichi, T., 2017. Courtesy food sharing characterized by begging for social bonds in wild bonobos. In: Hare, B., Yamamoto, S. (Eds.), Bonobos: Unique in Mind, Brain and Behavior. Oxford University Press, Oxford, pp. 125–139.

Yang, Z., 2007. PAML4: Phylogenetic analysis by maximum likelihood. Mol. Biol. Evol. 24, 1586–1591.

Yang, Z., Nielsen, R., 2002. Codon-substitution models for detecting molecular adaptation at individual sites along specific lineages. Mol. Biol. Evol. 19, 908–917.

Yates, A.D., Achuthan, P., Akanni, W., Allen, J., Allen, J., Alvarez-jarreta, J., Amode, M.R., Armean, I.M., Azov, A.G., Bennett, R., Marug, C., Cummins, C., Bhai, J., Billis, K., Boddu, S., Davidson, C., Dodiya, K., Fatima, R., Gall, A., Giron, C.G., Gil, L., Grego, T., Haggerty, L., Haskell, E., Hourlier, T., Izuogu, G., Janacek, S.H., Juettemann, T., Kay, M., Lavidas, I., Le, T., Lemos, D., Martinez, J.G., Maurel, T., Mcdowall, M., Mcmahon, A., Mohanan, S., Moore, B., Nuhn, M., Oheh, D.N., Parker, A., Parton, A., Patricio, M., Sakthivel, M.P., Imran, A., Salam, A., Schmitt, B.M., Schuilenburg, H., Sheppard, D., Sycheva, M., Szuba, M., Taylor, K., Thormann, A., Threadgold, G., Vullo, A., Walts, B., Winterbottom, A., Zadissa, A., Chakiachvili, M., Flint, B., Frankish, A., Hunt, S.E., Iisley, G., Kostadima, M., Langridge, N., Loveland, J.E., Martin, J., Morales, J., Mudge, J.M., Muffato, M., Perry, E., Ruffier, M., Trevanion, S.J., Cunningham, F., Howe, K.L., Zerbino, R., Flicek, P., 2020. Ensembl 2020. Nucleic Acids Res. 48, 682–688.

Young, W.S., Gainer, H., 2003. Transgenesis and the study of expression, cellular targeting and function of oxytocin, vasopressin and their receptors. Neuroendocrinology 78, 185–203.

Zhang, J., Yan, P., Li, Y., Cai, X., Yang, Z., Miao, X., Chen, B., Li, S., Dang, W., Jia, W., Zhu, Y., 2018. A 35.8 kilobases haplotype spanning *ANKK1* and *DRD2* is associated with heroin dependence in Han Chinese males. Brain Res. 1688, 55–64.

Zhang, S., Zhang, M., Zhang, J., 2014. Association of *COMT* and *COMT - DRD2* interaction with creative potential. Front. Hum. Neurosci. 8, 1–9.

Zhang, Y., Wu, C., Chang, H., Yan, Q., Wu, L., Yuan, S., Xiang, J., Hao, W., Yu, Y., 2018. Genetic variants in oxytocin receptor gene (*OXTR*) and childhood physical abuse collaborate to modify the risk of aggression in chinese adolescents. J. Affect. Disord. 229, 105–110.